Clinical Study Protocol

AN OPEN-LABEL, LONG-TERM SAFETY STUDY OF SD-809 (DEUTETRABENAZINE) FOR THE TREATMENT OF MODERATE TO SEVERE TARDIVE DYSKINESIA

Study Number SD-809-C-20

NCT02198794

Protocol with Amendment 07 Approval Date: 02 May 2018

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EUDRACT No.: 2014-001891-73

Amendment 07 (Part C Study)

(Specific to Investigators in EU Countries)

02 May 2018

Development Phase: 3

STUDY CONTACTS

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PROTOCOL SYNOPSIS

PROTOCOL	SD-809-C-20
TITLE	An Open-Label, Long-Term Safety Study of SD-809 (deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia
PHASE	3 (Safety)
INDICATION	Treatment of drug-induced tardive dyskinesia (TD)
NO. SITES	Approximately 80
OBJECTIVES	• To evaluate the safety and tolerability of long-term maintenance therapy with SD-809 • To evaluate the efficacy of long-term maintenance therapy of SD-809 to reduce the severity of abnormal involuntary movements of TD • To evaluate the persistence of the therapeutic effect of SD-809
STUDY POPULATION	Male and female adult subjects with moderate to severe drug-induced TD who have successfully completed a previous placebo-controlled efficacy study of SD-809 for the treatment of TD with the Sponsor will be enrolled.
STUDY DESIGN	This is an open-label, single-arm study in which subjects with moderate to severe TD who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for the treatment of moderate to severe TD) will be invited to participate. Informed consent/assent (Part A) will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of the subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Informed consent/assent for Part B will be obtained after Amendment 06 implementation and before any study procedures related to Part B are performed. Informed consent/assent for Part C will be obtained after Amendment 07 implementation and before any study procedures related to Part C are performed. Subjects who do not sign the informed consent/assent for Part C will complete the study at Part B Follow-up Call. Subjects who have successfully completed a parent study may be eligible to enroll into this study after they complete a 1-week washout period and the final evaluation in the parent study. To reduce subject burden, after obtaining informed consent/assent, some data collected in the parent study will be used in Study SD-809-C-20 and will provide some of the baseline data for Study SD-809-C-20 (see Schedule of Events). For example, in addition to assessments completed for the SD-809-C-18 Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit. **Part A:** **Titration Period (up to 6 weeks):** As subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo SD-809 dose titration in this study. During titration, the Investigator, in consultation with the subject, will determine when an adequate level of dyskinesia control has been achieved. The dose of SD-809 should be adjusted (upward or downward), in

STUDY DESIGN (continued)	increments of 6 mg per day (up to once per week), until there is adequate control of dyskinesia, the subject experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meets the criteria for a serious adverse event), or the maximal allowable dose is reached. If a subject experiences a clinically significant adverse event attributable to SD-809, the Investigator will determine if a dose reduction, dose suspension, or withdrawal from the study is necessary. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2 to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. ***Although subjects will enter the Long-Term Treatment Period after Week 2, titration should continue through Week 6 to optimize dose.*** **Long-Term Treatment Period (Week 3 until the last dose in Part A**): During long-term treatment, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a dose level that adequately controls dyskinesia and is well tolerated by the Week 6 visit should have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Interactions with the clinical site for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at the last dose of Part A (completion of Part A=Week 158 or beginning of Part B after Amendment 06 implementation). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and only in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's (if appropriate) reports of adverse events and dyskinesia control, as well as information from rating scales and safety evaluations, when available. If warranted, study sites are encouraged to conduct periodic phone calls with subjects to ensure adherence to the treatment regimen and retention of unused drug containers. Subjects who have been on a stable dose of SD-809 and any concomitant dopamine receptor antagonist (DRA) for a minimum of 4 weeks will be invited to participate in the Randomized Withdrawal Period (Part B) at the next routine visit at the site after approvals from IRB/Ethics Committee and as required by country regulations. If the subject chooses to participate in Part B, then participation in Part A will end. Subjects who decline to participate in Part B will continue in Part A until Week 158. Subjects who decline participation in Part B will be given an ongoing option to participate at subsequent study visits. **Part B:** Part B will consist of a double-blind, randomized withdrawal period; treatment with SD-809; and post-treatment safety follow-up. The Randomized Withdrawal Period will be 1 week (+3 days maximum) in duration and will consist of 2 visits, the Pre-withdrawal Visit and the Post-withdrawal Visit. After the Randomized Withdrawal Period, the subject will resume treatment with SD-809 on the prior established dose for an additional 12 weeks until end of treatment (EOT). A follow-up telephone call will occur 4 weeks after EOT. At the beginning of the Randomized Withdrawal Period, subjects will be randomized

	in a blinded fashion to either SD-809 (current dose) or placebo in a 1:1 ratio stratified by DRA usage. Up to 194 subjects (active subjects as of the approval date of Amendment 06) will be randomized (SD-809 or placebo). Subjects will be required to sign a written informed consent. Subjects will need to be on a stable dose of SD-809 and any concomitant DRA for a minimum of 4 weeks before starting the Randomized Withdrawal Period. Subjects will be scheduled to return 1 week (+3 days maximum) after the Pre-withdrawal Visit of the Randomized Withdrawal Period for efficacy and safety assessments. At the end of this period, subjects will continue treatment with SD-809 at the previous dose administered before the Randomized Withdrawal Period (last dose in Part A). Treatment with SD-809 will continue for 12 weeks until the EOT visit. Video ratings of the Abnormal Involuntary Movement Scale (AIMS) will occur at the Pre-withdrawal Visit, the Post-withdrawal Visit, and the EOT/early termination (ET) visit. **Part C:** Part C will consist of a 52-week period of reduced burden safety assessments, for subjects in the EU countries. Subjects can only enter Part C once they have entered and completed Part B. The Part B EOT will coincide with Part C Visit 1 for those subjects who are willing to continue with the 52-week reduced burden safety assessment period. **Post-Treatment Safety Follow-up:** **Part A**: Subjects who do not participate in Part B will continue in Part A, discontinue study drug at the Week 158 visit, and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week follow-up period, subjects should continue to not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage. Subjects who discontinue study drug in Part A will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET. **Part B**: Subjects who complete the Randomized Withdrawal Period and subsequent 12 weeks of treatment will complete an EOT visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT. Subjects in EU countries may choose to enroll in Part C, in which case Part B EOT will coincide with Part C Visit 1. Subjects who discontinue study drug in Part B will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET. **Part C**: Subjects who complete the 52 weeks of reduced burden safety assessments period

	will complete a Part C EOT Visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since Part C EOT. Subjects who discontinue study drug in Part C will complete an ET visit, a follow-up clinic visit 1 week later for safety evaluation, and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.
FORMULATION	SD-809 tablets will be provided in dosage strengths of 6, 9, 12, 15, and 18 mg. During dose adjustment/titration in Part A, SD-809 will be supplied in weekly blister cards. During long-term treatment, SD-809 will be supplied in 30-count bottles. During the blinded Randomized Withdrawal Period, SD-809 will be supplied in 20-count bottles, all of which are identical in size, shape, and color (white), whereas during long-term treatment, SD-809 will be supplied in 30-count bottles. Placebo tablets are identical in appearance to the SD-809 tablets and contain the same inactive ingredients as the SD-809 tablets. During Part C, SD-809 will be supplied in 30-count bottles.
DOSE REGIMEN	Study drug will be administered as follows: • All treatment regimens will be administered twice daily (BID) with meals, approximately 10 hours apart during the day. • The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the parent trial. Prior treatment assignment from the parent trial will remain blinded. • The maximum total daily dose of SD-809 is based on body weight: o If body weight <100 kg, the maximum daily dose is 48 mg/day (24 mg BID) unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum total daily dose is 36 mg/day. o If body weight ≥100 kg the maximum daily dose is 60 mg/day (30 mg BID) unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 42 mg/day • Daily doses will be administered according to instructions provided in the Pharmacy Manual. • During the titration period, the dose of SD-809 should be increased on a weekly basis in increments of 6 mg per day until: o There is adequate control of dyskinesia; o The subject experiences a protocol defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meets the criteria for a serious adverse event); or o The maximal allowable dose is reached. • If a subject experiences a clinically significant adverse event attributable to SD-809, the Investigator will determine if a dose reduction or suspension is necessary. <u>Part A</u> <u>Long-Term Treatment</u>: For all subjects participating in the Long-Term Treatment Period, the dose of SD-809 may be adjusted (upward or downward) in increments of 6 mg per day, if necessary, to optimize dyskinesia control while minimizing adverse events. However, such changes in dose may not occur more frequently than once per week. In the case of the

DOSE REGIMEN (continued)	addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, bupropion), a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. Part B Double-Blind, Randomized Withdrawal Period: Subjects in the Randomized Withdrawal Period will continue to receive their current dose of SD-809 or will receive matching placebo. At the end of the Randomized Withdrawal Period, subjects will continue with, or return to, the same dose of SD-809 taken before the Randomized Withdrawal Period (last dose in Part A), beginning the day after the Post-withdrawal Visit and continuing for 12 weeks. Subjects who do not return for the Post-withdrawal Visit within the 10 days (1 week [+3 days maximum]) may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary). Part C 52-Week Treatment Period: Subjects in Part C will continue treatment with SD-809 at the dose administered during the 12-week open-label treatment period of Part B (last dose in Part B), unless they will experience a delay in the completion of all the activities related to Part B EOT Visit, especially of study drug dispensation, in which case they may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor.
SAMPLE SIZE	Approximately 330 subjects (eligible subjects who completed a previous controlled study of SD-809 for treatment of moderate to severe TD) may enroll in Part A. During the Randomized Withdrawal Period in Part B, there will be up to 194 subjects randomized (SD-809 or placebo). Approximately 102 subjects may enroll in Part C conducted in the EU countries.
INCLUSION CRITERIA	1. Subject is at least 18 years of age at Screening. 2. Subject has successfully completed[a] Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for treatment of moderate to severe TD. 3. Subject has a history of using a DRA for at least 3 months (or 1 month in subjects 60 years of age and older). 4. Subject has a clinical diagnosis of TD and has had symptoms for at least 3 months prior to Screening. 5. For subjects with underlying psychiatric illness: • Subject is psychiatrically stable and has had no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before Screening (45 days for antidepressants). • Subjects on long-acting (depot) medications have been on stable therapy (dose, frequency) for ≥3 months before Screening. • Subject has a health care provider who is aware of the subject's participation in the trial and does not anticipate any changes to the

[a] Successful completion is defined as (1) study participation through Week 13 (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator, and (3) the subject has no ongoing AEs that are serious or severe in intensity or are expected to interfere with safety evaluations in this study.

	subject's treatment regimen (drug, dose, frequency) in the next 3 months. 6. Subject has a history of being compliant with prescribed medications. 7. Subject is able to swallow study drug whole. 8. Subject has provided written, informed consent or, if subject lacks the capacity to provide informed consent, a legally authorized representative (LAR) has provided written informed consent and the subject has provided assent. 9. In the opinion of the Investigator, the subject lives in a stable environment, and has adequate supervision when necessary to comply with all study procedures, attend all study visits, and safely participate in the trial. 10. Subject has sufficient reading skills to comprehend the subject-completed rating scales. 11. Female subjects of childbearing potential[b] agree to use one of the following acceptable methods of contraception from Screening through study completion if sexually active: • IUD or intrauterine system in place for at least 3 months prior to screening; • Subject or partner using barrier method (e.g., condom, diaphragm, or cervical cap) with spermicide from Screening through study completion; • Partner has a documented vasectomy >6 months prior to enrollment; • Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to Screening.
EXCLUSION CRITERIA	1. Subject has received tetrabenazine within 7 days of Baseline. 2. Subject has received any of the following medications within 30 days of Baseline: • Reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Baseline), and medications with strong anticholinergic activity (e.g., trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden) • Metoclopramide, promethazine, and prochlorperazine • Stimulants (e.g., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine.), or monoamine oxidase inhibitors (MAOIs) • Levodopa or dopamine agonists 3. Subject has a neurological condition other than TD that may interfere with assessing the severity of dyskinesias. 4. Subject has a serious untreated or undertreated psychiatric illness at Baseline. 5. Subject has active suicidal ideation at Baseline. 6. Subject has a history of any of the following within 6 months of Baseline: • Previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence at the time of suicidal thought • Previous preparatory acts to commit suicide or suicidal behavior • A previous actual, interrupted, or aborted suicide attempt 7. Subject has a score ≥11 on the depression subscale of the Hospital Anxiety and

[b] Non-childbearing potential for females is defined as postmenopausal (amenorrheic for at least 1 year and serum follicle stimulating hormone (FSH) level consistent with postmenopausal status), or a documented hysterectomy; bilateral oophorectomy; or bilateral tubal ligation ≥6 months prior to study initiation.

EXCLUSION CRITERIA (continued)	Depression Scale (HADS) at Baseline. 8. Subject is developmentally disabled or has evidence of dementia. 9. Subject has an unstable or serious medical illness at Baseline. 10. Subject has history (within 3 months) or presence of violent behavior. 11. Subject has a Fridericia-corrected QT interval (QTcF) value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block [RBBB]) on 12-lead electrocardiogram (ECG) at Baseline. 12. Subject has evidence of hepatic impairment at Screening of the parent study, as indicated by: • Aspartate transaminase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) • Alkaline phosphatase (ALP) or total bilirubin (TBil) >2 times the ULN o Note: Subjects with Gilbert's Syndrome are eligible to participate if approved by the Medical Monitor. o Note: Subjects with abnormalities in two or more of these analytes (AST, ALT, ALP, TBil) must be approved by the Medical Monitor to be enrolled. • Prothrombin time >17 seconds (i.e., prothrombin time prolonged >4 seconds over the ULN) • Positive Hepatitis B surface antigen (HBsAg) 13. Subject has evidence of significant renal impairment at Screening of the parent study, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockroft-Gault formula. 14. Subject has known allergy to tetrabenazine or to any of the components of SD-809. 15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18, Study SD-809-C-23, or any other eligible SD-809 parent study) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer. 16. Subject is pregnant or breastfeeding at Baseline. 17. Subject acknowledges present use of illicit drugs at Baseline. 18. Subject has a history of alcohol or substance abuse in the previous 12 months, as defined in the DSM-V, or subject is unable to refrain from substance abuse throughout the study.
SAFETY PARAMETERS	Safety and tolerability will be assessed throughout the study by monitoring the following parameters: • Adverse events • Clinical laboratory tests • Physical examination • Vital signs • 12-lead ECGs • Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor examination) • Barnes Akathisia Rating Scale (BARS) • HADS • Columbia Suicide Severity Rating Scale (C-SSRS) • Epworth Sleepiness Scale (ESS) • Montreal Cognitive Assessment (MoCA©)

SAFETY ENDPOINTS	<u>The following safety endpoints will be assessed in Part A</u> • Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, adverse events leading to withdrawal during the following periods: - Overall - During titration - During long term treatment • Observed values and changes from Baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes from Baseline in vital signs • Observed values in ECG parameters and abnormal findings • Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms • Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA© • Duration of time to achieve stable dosing of SD-809 <u>The following secondary safety endpoints will be assessed in Part B</u> • Secondary safety endpoints: - Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, and adverse events leading to withdrawal - Observed values and changes from start of randomized withdrawal in clinical laboratory parameters (hematology, chemistry, and urinalysis) - Observed values and changes from start of randomized withdrawal in vital signs - Observed values in ECG parameters and abnormal findings - Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from baseline in QTcF of >30 ms or >60 ms - Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA© <u>The following secondary safety endpoints will be assessed in Part C</u> • Secondary safety endpoints: - Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, and adverse events leading to withdrawal from start of Part C - Observed values and changes in vital signs from start of Part C - Observed values and changes in C-SSRS from start of Part C - Observed values in ECG parameters and abnormal findings from start of Part C - Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from baseline in QTcF of >30 ms or >60 ms from start of Part C

EFFICACY MEASURES	Efficacy Measures during Part A: • The change in AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by the site rating. • The proportion of subjects who are a treatment success based on the Clinical Global Impression of Change (CGIC) at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study. • The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline of this study at each visit that this is measured. • The change in the modified Craniocervical Dystonia (CDQ-24) score from Baseline of this study at each visit that this is measured. • The proportion of subjects who are a treatment success based on the Patient Global Impression of Change (PGIC) at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study. • The percent change in AIMS score from Baseline of this study at each visit that this is measured. The following efficacy measure will be assessed during Part B (Double-Blind, Randomized Withdrawal Period): • Primary efficacy endpoint: change from Pre-withdrawal Visit AIMS scores (items 1 through 7) as assessed by blinded central video rating to the Post-withdrawal Visit between subjects treated with SD-809 and subjects treated with placebo.
STATISTICS	<u>Safety:</u> Safety data will be summarized descriptively for the overall population and based on prior treatment (SD-809 or placebo) in the parent study. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. The nature, frequency, and severity of adverse events will be tabulated for all subjects combined and by prior treatment. Baseline, within study, end of study, and change-from-baseline values for clinical laboratory evaluations and vital signs will be summarized as appropriate. Treatment-emergent adverse events and laboratory, vital sign, and ECG parameters will be summarized. In addition, change from baseline will be summarized for laboratory and vital sign parameters. Shift tables will be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized. Descriptive statistics of change-from-baseline will use the Baseline from the present study and will be specified in the Statistical Analysis Plan. <u>Efficacy:</u> Descriptive statistics will be used to summarize efficacy measures for the overall population and based on prior treatment (SD-809 or placebo) in the parent study. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. Descriptive statistics of change-from-baseline will utilize Baseline from the present study (SD-809-C-20 Baseline). <u>Double-Blind, Randomized Withdrawal Period Power and Sample Size:</u> It is estimated that approximately 91 subjects per arm will enable a power of at least 90% to detect a beneficial effect of 1.4 points or more in the change from pre-withdrawal to post-withdrawal in centrally read AIMS when the SD-809 arm is

	compared to placebo, assuming a standard deviation of 2.9 and a 2-sided type I error rate of 5%. Analysis of the change in centrally read AIMS score during the Randomized Withdrawal Period (from the Pre-withdrawal Visit to the Post-withdrawal Visit) will use an analysis of covariance (ANCOVA) model with the change in AIMS score as the dependent variable. The model will include randomized withdrawal treatment group, AIMS score at the Pre-withdrawal Visit, and DRA status at the Pre-withdrawal Visit as fixed effects. The least squares means of the change in AIMS score will be compared between the SD-809 treatment and placebo groups using a 2-sided test at the alpha=0.05 level of significance. In addition, actual values and changes in AIMS score will be summarized using descriptive statistics. The primary efficacy analysis will be tested at the α=0.05 level. If less than 135 subjects are enrolled into the randomized withdrawal portion of the study, inferential statistics will not be provided as the study will be insufficiently powered to detect a treatment effect given the sample size assumptions.

SCHEDULE OF EVENTS

Part A

	Screening		Year 1										Year 2				Year 3				Follow-up clinic visit	Follow-up Call	Unscheduled	
			Titration Period		Long-Term Treatment Period																			
Study Week[l] →	**Prior Data from Parent Study†**	**Base-line‡**	**1**	**2**	**3**	**4**	**5**	**6**	**15**	**28**	**41**	**54**	**67**	**80**	**93**	**106**	**119**	**132**	**145**	**158[10]/ET[11]**	**159 or 1 week after ET**	**162 or 4 weeks after ET**		
Visit Window (days)		+3	± 1		± 3																			
Activity Visit Type →		V	TC	V	TC	V	TC	V	V	V	V	V	V	V	V	V	V	V	V	V	V	TC	V	TC
Evaluate/Adjust Dose			X	X	X	X	X	X															X[3]	X[3]
Informed Consent/Assent		X§																						
Screening/ Demographics	*																							
Inclusion/ Exclusion Criteria		X																						
Update Medical History		X																						
Vital Signs/ Weight		**		X		X		X[2]	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X[2]	X		X	
Physical Examination	*									X[4]		X				X				X				
Complete Neurological Exam	*											X				X				X				
Height	*																							
12-lead ECG		X		X		X		X		X	X	X				X				X			X[3,9]	
Blood Sampling for PK																							X[7,8]	
Chemistry/ Hematology/ UA	*							X		X		X				X				X			X[3]	
Blinded CYP2D6 Genotype[1]	*																							
Pregnancy Test		U								U		U				U				U				
AIMS		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Video Recording of AIMS		X						X	X	X	X	X				X				X				

	Screening		Year 1										Year 2				Year 3				Follow-up clinic visit	Follow-up Call	Unscheduled	
			Titration Period		Long-Term Treatment Period																			
Study Week[1] →	**Prior Data from Parent Study†**	**Base-line‡**	**1**	**2**	**3**	**4**	**5**	**6**	**15**	**28**	**41**	**54**	**67**	**80**	**93**	**106**	**119**	**132**	**145**	**158[10]/ET[11]**	**159 or 1 week after ET**	**162 or 4 weeks after ET**		
Visit Window (days)		+3	± 1		± 3																			
Activity Visit Type →		V	TC	V	TC	V	TC	V	V	V	V	V	V	V	V	V	V	V	V	V	V	TC	V	TC
UPDRS Part III - Motor		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[3]	
BARS		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[3]	
HADS		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
C-SSRS[5]		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
ESS		**		X		X		X	X	X	X	X	X	X	X		X		X	X			X[3]	
CGIC						X		X	X	X	X	X	X	X	X	X	X	X	X					
PGIC						X		X	X	X	X	X	X	X	X	X	X	X	X					
MoCA©		X						X	X	X	X	X	X	X	X		X		X					
Modified CDQ-24		X						X	X	X	X	X				X				X				
Dispense/Order Study Drug[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X[3]	X[3]
Assess Study Drug Accountability/ Compliance				X		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Assess AEs	*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Meds	*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluate Dyskinesia Control (subject/ caregiver)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

SCHEDULE OF EVENTS (Part A) KEY

[V] Clinic Visit

[TC] Telephone Contact

[ET] Early Termination Visit

[U] Urine pregnancy test for women of childbearing potential only

Abbreviations: AEs, adverse events; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; MoCA©, Montreal Cognitive Assessment; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SAE, serious adverse event; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale.

‖ All stable subjects will be invited to participate in Part B after Amendment 06 implementation regardless of current study week. Subjects will need to be on a stable dose of SD-809 and any concomitant dopamine receptor antagonist for a minimum of 4 weeks before starting the Double-Blind, Randomized Withdrawal Period.

† After Informed Consent is obtained, prior data from the parent study will be used in this study as part of screening information as detailed in the informed consent/assent.

‡ Data from the Week 13 evaluation of the parent study will provide some of the Baseline data for the present study, although such data will not become available for this study until informed consent/assent has been provided.

§ May be performed up to 30 days in advance of Baseline

* Data (Week 12 or earlier) from the parent study will be used in this study as part of screening information.

** Data (Week 13) from the parent study will be used as part of Baseline assessment. Additional specific activities required at this visit are denoted by an "X"

1 Assessment transferred from Screening or Baseline evaluation in the parent study.

2 Perform orthostatic blood pressure and pulse after subject is in standing position for at least 3 minutes.

3 Assessments to be completed at Investigator's discretion.

4 Brief physical examination, which includes evaluation of the cardiovascular, respiratory, and abdominal systems.

5 The C-SSRS Since Last Visit version is administered at all visits.

6 Study medication supply will be ordered (see Operations Manual for further details).

7 Subjects who experience an SAE should have a blood sample collected for pharmacokinetic assessment as soon as possible after the SAE and within 48 hours of last dose of study drug, if possible.

8 Subjects who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected within 48 hours of the last dose of study drug for future pharmacokinetic assessment of α- and β-HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor.

9 Subjects undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring (see Section 6.7.1).

10 Subjects who have been on a stable dose of SD-809 and any concomitant dopamine receptor antagonist for 4 weeks will be invited to participate in the Randomized Withdrawal Period (Part B). If the subject chooses to participate in Part B, then participation in Part A will end.

11 Subjects will complete a follow-up visit 1 week after ET and a Follow-up Call 4 weeks after ET.

SCHEDULE OF EVENTS
Part B

	Randomized Withdrawal Period		**Open-label Treatment**	**Follow-up**			
	Part B Pre-withdrawal Visit	**Part B Post-withdrawal Visit[11]**	**EOT[2]/ET**	**Follow-up clinic visit (ET only)**	**Follow-up Call**	**Unscheduled**	
Study Week →	**After Amendment 06 Implementation[1,12]**	**+1 Week**	**12 Weeks after Post-withdrawal Visit**	**1 Week after ET**	**4 Weeks after EOT/ET**		
Visit Window (days)		+3	±3				
Activity Visit Type →	V	V	V	V	TC	V	TC
Evaluate/Adjust Dose[3]						X[4]	X[4]
Informed Consent/Assent	X[5]						
Randomization via IRT	X						
Screening/ Demographics							
Inclusion/ Exclusion Criteria							
Update Medical History							
Vital Signs/ Weight	X[6]	X	X[6]	X		X	
Physical Examination			X				
Complete Neurological Exam			X				
12-lead ECG	X	X	X			X[4,11]	
Blood Sampling for PK		X				X[9,10]	
Chemistry/ Hematology/ UA	X	X	X			X[4]	
Pregnancy Test	U		U				
AIMS	X	X	X	X			
Video Recording of AIMS	X	X	X				
UPDRS Part III - Motor	X	X	X	X		X[4]	
BARS	X	X	X	X		X[4]	
HADS	X	X	X	X		X	
C-SSRS[7]	X	X	X	X		X	
ESS	X	X	X	X		X[4]	
CGIC							
PGIC							

	Randomized Withdrawal Period		Open-label Treatment	Follow-up			
	Part B Pre-withdrawal Visit	**Part B Post-withdrawal Visit[11]**	**EOT[2]/ET**	**Follow-up clinic visit (ET only)**	**Follow-up Call**	**Unscheduled**	
Study Week →	**After Amendment 06 Implementation[1,12]**	**+1 Week**	**12 Weeks after Post-withdrawal Visit**	**1 Week after ET**	**4 Weeks after EOT/ET**		
Visit Window (days)		+3	±3				
Activity Visit Type →	V	V	V	V	TC	V	TC
MoCA©	X	X	X				
Modified CDQ-24							
Dispense/Order Study Drug[8]	X	X				X[4]	X[3]
Assess Study Drug Accountability/ Compliance[13,14]	X	X	X				
Assess AEs	X	X	X	X	X	X	X
Assess Concomitant Meds	X	X	X	X	X	X	X
Evaluate Dyskinesia Control (subject/caregiver)	X	X	X	X		X	X

SCHEDULE OF EVENTS (Part B) KEY

[V] Clinic Visit

[TC] Telephone Contact

[EOT] End of Treatment

[ET] Early Termination Visit

[U] Urine pregnancy test for women of childbearing potential only

Abbreviations: AEs, adverse events; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; IRT, MoCA©, Montreal Cognitive Assessment; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SAE, serious adverse event; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale.

1 Assessments required for the Pre-withdrawal Visit will be those required for the next scheduled visit, or visit as determined by the Investigator, after Amendment 06 implementation and subject consent for Part B.

2 The EOT visit will occur 12 weeks after the Post-withdrawal Visit.

3 Titration is not permitted during the Randomized Withdrawal Period and will be allowed after return to open-label dosing.

4 Assessments to be completed at Investigator's discretion.

5 Subjects who do not sign the informed consent for Part B will continue participation in Part A. Subjects who decline participation in Part B will be given an ongoing option to participate at subsequent study visits.

6 Perform orthostatic blood pressure and pulse.
7 The C-SSRS Since Last Visit version is administered at all visits.
8 Study medication supply will be ordered (see Operations Manual for further details).
9 At the discretion of the Principal Investigator and/or Medical Monitor, subjects who experience an SAE may have a blood sample collected for pharmacokinetic assessment after experiencing the SAE. All such blood samples will be collected within 48 hours of last dose of study drug.
10 Subjects who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected within 48 hours of the last dose of study drug for future pharmacokinetic assessment of α- and β-HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor.
11 Subjects undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring (see Section 6.7.1).
12 If the subject chooses to participate in Part B, the first visit will be the subject's next scheduled visit, or as soon as possible, as determined by the Investigator, after Amendment 06 implementation. The Post-withdrawal Visit will occur 1 week (+3 days maximum). If the Post-withdrawal Visit is >3 days beyond the 1-week time period, the subject may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary) per the guidelines in Table 3. After the Randomized Withdrawal Period, the subject will continue on or return to previous (before placebo) SD-809 dose.
13 Prior to the Pre-withdrawal Visit, the Investigator or designated site staff must place a call to remind the subject to bring all remaining study drugs to the visit. The Investigator or designated site staff must collect the study drug(s) from the subject and conduct drug accountability.
14 Prior to the Post-withdrawal Visit, the Investigator or designated site staff must place a call to remind the subject to bring all remaining study drugs to the visit. The Investigator or designated site staff must collect the study drug(s) from the subject and conduct drug accountability.

SCHEDULE OF EVENTS
Part C EU Countries (Slovakia and Poland)

	Part C[1]		**EOT/ET**	**Follow-up Clinic Visit (ET Only)**	**Follow-up Call**	**Unscheduled**	
Study Week →	**After Amendment 07 Implementation[2]**		**52 Weeks after Part C V1**	**1 Week after ET**	**4 Weeks after Part C EOT/ET**		
Visit Window (days)	+7	Part C V2, V3, V4 (q13 weeks) ±7 days	±7 days	±3 days	±3 days		
Activity Visit Type →	**Part B EOT/Part C V1[3]**	**V**	**V**	**V**	**TC**	**V**	**TC**
Informed Consent/Assent	X[4]						
Screening/ Demographics							
Inclusion/ Exclusion Criteria							
Update Medical History							
Vital Signs/ Weight[5]	X	X	X	X		X	
Physical Examination	X	X	X				
Complete Neurological Exam	X		X				
12-lead ECG	X	X	X			X[11,12]	
Blood Sampling for PK							
Chemistry/Hematology/UA	X						
Pregnancy Test[6]	U	U	U				
AIMS	X						
Video Recording of AIMS	X						
UPDRS Part III - Motor	X						
BARS	X						
HADS	X						
C-SSRS[7]	X	X	X	X		X	
ESS	X						
MoCA©	X						
Dispense Study Drug[8]	X[9]	X				X[12]	

	Part C[1]		EOT/ET	Follow-up Clinic Visit (ET Only)	Follow-up Call	Unscheduled	
Study Week →	**After Amendment 07 Implementation[2]**		**52 Weeks after Part C V1**	**1 Week after ET**	**4 Weeks after Part C EOT/ET**		
Visit Window (days)	+7	Part C V2, V3, V4 (q13 weeks) ±7 days	±7 days	±3 days	±3 days		
Activity Visit Type →	**Part B EOT/Part C V1[3]**	**V**	**V**	**V**	**TC**	**V**	**TC**
Assess Study Drug Accountability/ Compliance[10]		X	X				
Assess AEs	X	X	X	X	X	X	X
Assess Concomitant Meds	X	X	X	X	X	X	X
Evaluate Dyskinesia Control (subject/caregiver)	X						

SCHEDULE OF EVENTS (Part C) KEY

[V] Clinic visit

[TC] Telephone contact

[EOT] End of Treatment

[ET] Early Termination Visit

[U] Urine pregnancy test for women of childbearing potential only

Abbreviations: AEs, adverse events; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS, Epworth Sleepiness Scale; EU, European Union; HADS, Hospital Anxiety and Depression Scale; MoCA©, Montreal Cognitive Assessment; PK, pharmacokinetics; q13 weeks, every 13 weeks; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale; V1, Visit 1.

1 In the EU, if subjects reach the end of Part A, they may be enrolled in Part B and complete the randomized withdrawal and follow-up treatment of Part B and then enroll in Part C.

2 If the subject chooses to participate in Part C, the first visit will be combined with the EOT visit in Part B, after Amendment 07 implementation. The subject will continue with the current SD-809 dose.

3 One set of assessments will be performed for Part B EOT/Part C V1 (do not duplicate assessments).

4 Subjects who do not sign the informed consent/assent for Part C will complete the study at Part B Follow-up Call.

5 Perform orthostatic blood pressure and pulse at Part B EOT/Part C V1 and resting blood pressure and pulse at all other visits.

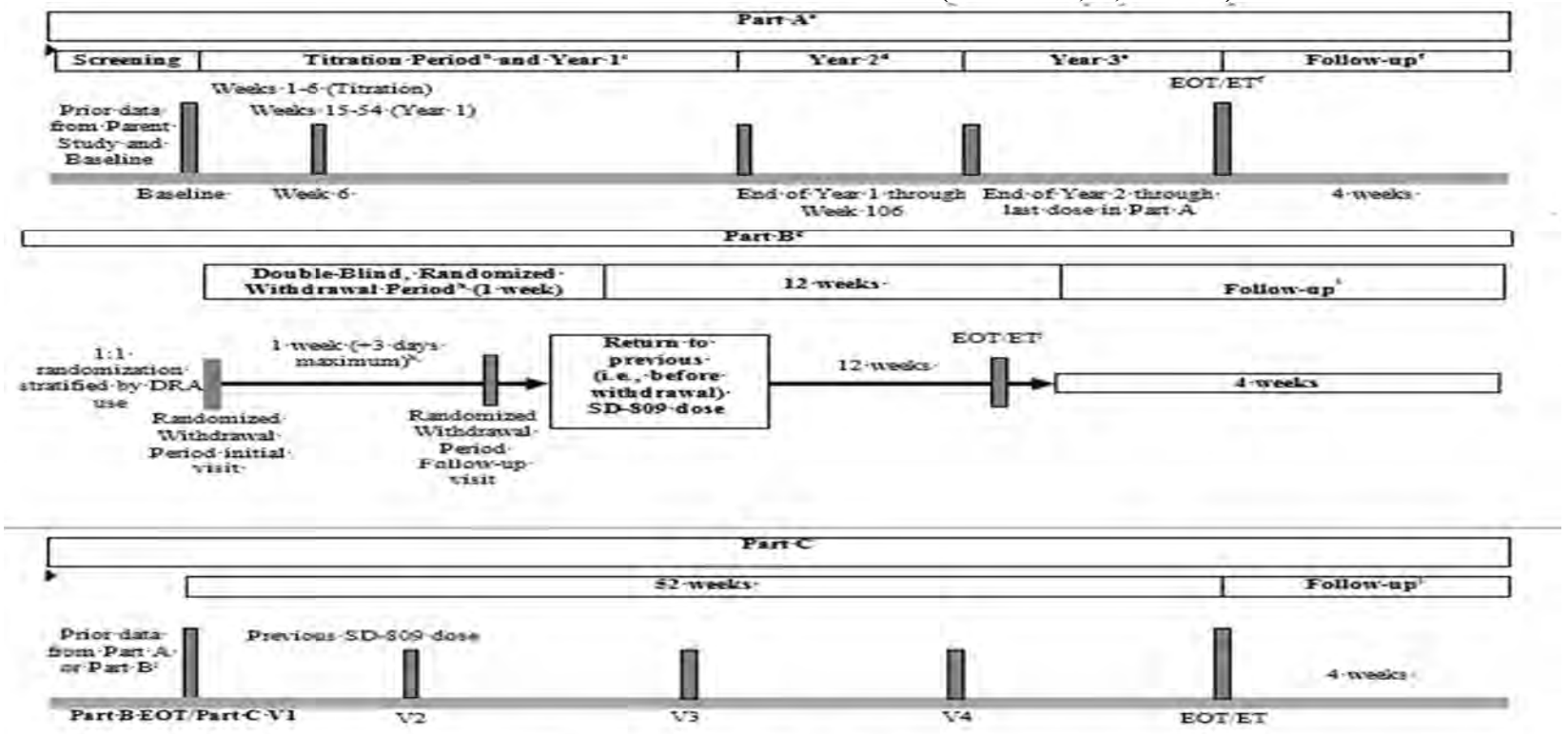
6 The pregnancy test will be done locally at the study site.

7 The C-SSRS Since Last Visit version is administered at all visits.

8 Study medication supply will be dispensed (see Operations Manual for further details).

9 Drug will dispensed for Part C V1.
10 Prior to each visit, the Investigator or designated site staff should call to remind the subject to bring all remaining study drugs to the visit.
11 Subjects undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring (see Section 6.7.1).
12 Assessments to be completed at Investigator's discretion.

STUDY SCHEMATIC DIAGRAM (PARTS A, B, AND C)



Abbreviation: DRA, dopamine receptor antagonist; EOT, end of treatment; ET, early termination.

[a] Subject participation will end at Week 158, at start of Part B (after after Amendment 06 implementation regardless of current study week), or ET. Subjects will need to be on a stable dose of SD-809 and any concomitant dopamine receptor antagonist for a minimum of 4 weeks before starting the Double-Blind, Randomized Withdrawal Period (Part B).

[b] Weeks 1 through 6 (telephone contact at Weeks 1, 3, and 5; clinic visit at Weeks 2, 4, and 6).

[c] Weeks 15 through 54 (clinic visits once every 13 weeks).

[d] Weeks 67 through 106 (clinic visits once every 13 weeks).

[e] Weeks 119 through 158 (clinic visits once every 13 weeks).

[f] Subjects who do not participate in Part B will continue in Part A until EOT at Week 158 or until ET, will complete a follow-up visit at Week 159 or 1 week after ET, and follow-up call at Week 162 or 4 weeks after ET.

[g] Subjects will need be on a stable dose of SD-809 and any concomitant DRA for a minimum of 4 weeks before starting the Randomized Withdrawal Period. The first visit of the Randomized Withdrawal Period of Part B (Pre-withdrawal Visit) will be the subject's next scheduled visit, or a visit as determined by the Investigator, after Amendment 06 implementation. The Post-withdrawal Visit will occur approximately 1 week after the scheduled visit. After the Post-withdrawal Visit, subjects will return to the previous (i.e., before withdrawal) dose of SD-809 and complete 12 more weeks of treatment before EOT.

[h] Subjects who do not complete the 1 week (+3 days maximum) will complete the ET visit.

[i] Follow-up after EOT is a follow-up telephone contact 4 weeks after EOT. Follow-up after ET consists of a clinic visit 1 week after ET and a telephone contact 4 weeks after ET.

[j] Subjects who completed Part B and complete EOT can be enrolled in Part C.

Note: An unscheduled visit will require a clinic visit or telephone call.

PROTOCOL APPROVAL PAGE

AN OPEN-LABEL, LONG-TERM SAFETY STUDY OF SD-809 (DEUTETRABENAZINE) FOR THE TREATMENT OF MODERATE TO SEVERE TARDIVE DYSKINESIA

Approved By: [redacted]

02 May 2018

Date

Vice President, TA Head, Specialty R&D
Teva Pharmaceuticals

[redacted]

Date

Coordinating Investigator for the Study

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LIST OF ABBREVIATIONS

Abbreviation	Definition
≤	less than or equal to
≥	greater than or equal to
°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPT	α-methyl-p-tyrosine
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under curve
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BPS	blepharospasm
BUN	blood urea nitrogen
C	carbon
CATIE	Clinical Antipsychotic Trials for Intervention Effectiveness
CD	cervical dystonia
CDQ-24	Craniocervical Dystonia Questionnaire
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
C_{max}	maximum concentration
CNS	central nervous system
eCRF	electronic case report form
EDC	electronic data capture
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CUTLASS1	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study

Abbreviation	Definition
CYP2D6	cytochrome P_{450} 2D6
CYP_{450}	cytochrome P_{450}
D, d	deuterium
DRA	dopamine receptor antagonist
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
ESS	Epworth Sleepiness Scale
EOT	End of treatment
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
g	grams
GCP	Good Clinical Practice
H	hydrogen
HADS	Hospital Anxiety and Depression Scale
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HD	Huntington's disease
HIV	human immunodeficiency virus
HTBZ	dihydrotetrabenazine
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
kg	kilogram
LAI	long-acting injectable
LAR	legally authorized representative

Abbreviation	Definition
LDH	lactate dehydrogenase
LTS	long-term safety
MAOI	monoamine oxidase inhibitor
MCV	mean cell volume
mg	milligram
mITT	modified intent-to-treat
mL	milliliter
MoCA©	Montreal Cognitive Assessment
ms	millisecond
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders & Stroke
O	oxygen
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	PR interval - measured from the beginning of the P wave to the beginning of the QRS complex
PR	prothrombin time
QRS	QRS duration (complex) - a structure on the ECG that corresponds to the depolarization of the ventricles
QT	QT interval - a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTcF	Fridericia-corrected QT interval
RBBB	right bundle branch block
RBC	red blood cell
SAE	serious adverse event
SOP	Standard Operating Procedure
SSRI	selective serotonin reuptake inhibitor
TBil	total bilirubin
TBZ	tetrabenazine
TD	Tardive dyskinesia
t_{max}	time of maximum drug concentration

Abbreviation	Definition
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VMAT	vesicular monoamine transporter

1. INTRODUCTION

1.1. Disease Background

Tardive dyskinesia (TD) is a serious delayed-onset hyperkinetic movement disorder that appears as a complication of prolonged use of dopamine receptor antagonists (DRAs) including antipsychotic agents (neuroleptics) and the prokinetic agent, metoclopramide. The clinical manifestations of TD include chorea, athetosis, dystonia, akathisia, stereotyped behaviors and occasionally, tremor. Although early identification of TD in younger outpatients can be associated with higher rates of recovery (50% to 90%; [Tarsy, 1983; Tarsy & Baldessarini, 1984]), TD is often irreversible, and can be significantly disabling and distressing to both patients and their family members and caregivers.

Although the pathophysiology of TD is not fully understood, the prevailing theory centers around the concept of dopamine-receptor hypersensitivity (Teo, Edwards, & Bhatia, 2012). Based on this theory, the chronic use of dopamine antagonists results in a gradual hypersensitization of dopamine receptors, leading to the clinical features of TD. Supporting this concept is the observation that increasing the dose of an antipsychotic drug temporarily suppresses the symptoms of TD, while withdrawing the antipsychotic or administering a dopamine agonist exacerbates the dyskinesia in the short term. In addition, the imbalance between D1 and D2 receptor-mediated effects in the basal ganglia has also been considered to be a contributing factor (Gerlach & Hansen, 1992; Trugman, 1998). The first-generation (typical) antipsychotics (i.e., haloperidol, chlorpromazine, fluphenazine, etc.), which are causally associated with TD, are potent inhibitors of the D2 receptors, resulting in excessive D1-mediated effects and high frequencies of extrapyramidal syndromes. Additionally, the development of TD has also been attributed to the possible destruction of striatal interneurons from excitotoxicity and oxidative stress, or more specifically, to the loss of the subpopulation of striatal GABAergic interneurons (Teo, et al., 2012).

The prevalence of TD can be difficult to establish, as the antipsychotic medications are known to cause, as well as mask, the symptoms of TD due to their hypokinetic effects (Tardive Dyskinesia Task Force, 1980; Tarsy & Baldessarini, 2006). Thus, prevalence rates in TD are frequently underestimated (Tarsy & Baldessarini, 2006). Nevertheless, the risk is substantial among patients exposed to DRBAs with rates ranging from 16% to 43% according to several studies reported between 1996 and 2002 (Tarsy & Baldessarini, 2006). The severity of TD often varies with behavioral and emotional arousal, and differences in population age, gender, treatment duration, and type and dose of antipsychotic medication can further confound the diagnosis (Kane, 2004; Lohr, 2008). Among outpatient schizophrenia patients treated with DRBAs, the prevalence of tardive syndromes is also high, and has been estimated to be 30% (American Psychiatric Association., 2000; Chouinard, Annable, Ross-Chouinard, & Mercier, 1988; Correll, Rummel-Kluge, Corves, Kane, & Leucht, 2009).

With the advent of the second-generation (atypical) antipsychotics (i.e., aripiprazole, clozapine, olanzapine, respiradone, quetiapine, and ziprasidone), which carry a lower risk for extrapyramidal syndromes, it has been suggested that the prevalence of TD should decline over time. However, a meta-analysis by Leucht and colleagues of 31 controlled studies comparing

older neuroleptics to newer, atypical agents found that only clozapine was associated with a significantly lower risk of acute extrapyramidal syndromes (Leucht, Wahlbeck, Hamann, & Kissling, 2003). Additionally, recent trials, including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS1), have not found significant differences in Abnormal Involuntary Movement Scale (AIMS) scores between patients taking first- or second-generation antipsychotics (Lieberman, 2005; Jones, 2006).

There are currently no approved medical therapies for the treatment of TD. Prevention and early detection are critical in the management of this disorder. Avoidance of treatment with antipsychotic medications and metoclopramide is the only definitive method of prevention. However, avoidance of antipsychotic therapies in patients with schizophrenia and other chronic psychoses is often not feasible. Evidence to support the withdrawal of, or switch from a typical to atypical DRBA in a patient who develops TD is limited at this time and must be weighed carefully against the risk of disease relapse and/or worsening of psychotic symptoms (Bhidayasiri et al., 2013).

Numerous pharmacologic therapies for TD have been evaluated, but few have shown more than modest clinical benefits in practice. According to recent evidence-based recommendations from the American Academy of Neurology (Bhidayasiri, et al., 2013), data do not support the use of diltiazem, galantamine, or eicosapentaenoic acid as treatments for TD. In addition, data are insufficient to either support or refute the use of several other agents previously studied in TD, including acetazolamide, bromocriptine, baclofen, vitamins/antioxidants (vitamins E, B6, thiamine, melatonin, or selegiline), most first or second-generation antipsychotic medications, levetiracetam, buspirone, and nifedipine. At the present time, only clonazepam, ginkgo biloba, amantadine, and tetrabenazine may be considered as treatment options for TD based on available data. As such, the medical need for developing safe and effective novel therapies in TD remains high.

1.2. Tetrabenazine

Tetrabenazine is approved in the United States (US), Canada and several European Union (EU) countries as a therapy for the treatment of chorea associated with Huntington's disease (HD). Tetrabenazine has also been used for several decades for the treatment of a variety of other hyperkinetic movement disorders including TD (Jankovic & Clarence-Smith, 2011; Kenney, Hunter, & Jankovic, 2007). In a single-blind study evaluating the efficacy and safety of tetrabenazine using a randomized videotape protocol pre- and post-treatment, significant reductions were observed post-treatment (mean dose 57.9 mg/d) in both the patient AIMS self rating and the AIMS motor subset evaluated by blinded videotape reviewers (Ondo, Hanna, & Jankovic, 1999). The patient AIMS self-rating scores improved 60.4% from a mean of 9.1 to 3.6 ($p<0.001$), while the AIMS motor subset scores improved 54.2% from 17.9 to 8.2 ($p<0.001$). In this study, tetrabenazine was well tolerated and all patients continued to the drug post-study. Overall, data on the treatment of TD with tetrabenazine in more than 400 patients have been reported across published studies (Jankovic & Clarence-Smith, 2011). On the basis of this clinical experience, several treatment algorithms have reported that tetrabenazine is effective for the treatment of TD, including the American Academy of Neurology evidence-based guidelines

in 2013 indicating that tetrabenazine may be considered in the treatment of tardive dyskinesia syndromes (Bhidayasiri, et al., 2013).

Tetrabenazine is rapidly and extensively converted in the liver by carbonyl reductase to alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ). These metabolites are potent and selective inhibitors of vesicular monoamine transporter (VMAT)-2, resulting in reduced storage and release of presynaptic dopamine, and are responsible for mediating the *in vivo* efficacy of orally administered tetrabenazine.

Details on the previous experience with tetrabenazine can be found in the SD-809 Investigator's Brochure (IB), which includes the tetrabenazine prescribing information for the treatment of chorea associated with HD.

1.2.1. Limitations of the Current Commercial Product

Tetrabenazine (Xenazine®, Nitoman®) is an immediate-release formulation. While generally effective in treating chorea of HD and other hyperkinetic movement disorders, tetrabenazine has limitations including:

- High peak concentrations of the active metabolites. Clinical experience in patients, and Phase 1 data in healthy volunteers, indicate that important adverse events of tetrabenazine, such as somnolence, akathisia, and anxiety are often associated with peak concentration after dosing.
- Short half-lives of the active metabolites and the attendant requirement to dose the immediate release formulation frequently. The rapid decline in plasma concentrations may lead to loss of efficacy at the end of the dosing interval. The fluctuation in plasma concentration, as indicated by high peak concentrations and low trough concentrations, necessitates more frequent dosing. Therefore, many patients must take tetrabenazine three times a day due to the short half-lives of the active metabolites, α-HTBZ and β-HTBZ. A less frequent dosing schedule is preferred as it may improve medication compliance.
- The active metabolites α- and β-HTBZ are either primarily (α) or exclusively (β) metabolized by cytochrome P_{450} 2D6 (CYP2D6). Polymorphisms in the CYP2D6 gene necessitate genotyping to prevent poor metabolizers from significantly greater exposure to the active drug moiety than extensive metabolizers.

To address the limitations of tetrabenazine, Auspex has developed a deuterated form of tetrabenazine (referred to as deutetrabenazine or SD-809) which is eliminated more slowly than tetrabenazine. As outlined in Section 1.4 and the IB, SD-809 has been shown to reduce plasma fluctuation and dosing frequency and thus, has the potential to improve overall tolerability compared with tetrabenazine.

1.3. Deuterium

Deuterium (D) is a naturally-occurring, non-radioactive stable isotope of hydrogen (H) which, due to the presence of a neutron, has twice the mass as H. Deuterium has a natural abundance of approximately 0.0156% of all H atoms (Baillie, 1981). The adult male body contains approximately 57% water (Guyton, 1991), the major source of H in the body (Chang, 2007). A 70 kg male contains approximately 39,900 g of water of which 0.0156% or 6.22 g is D_2O, yielding a naturally-occurring body content of 1.24 g of deuterium.

Small molecule drugs have been developed in which carbon (C)-H bonds have been replaced with C-D bonds (Kushner, Baker, & Dunstall, 1999). The increased mass of deuterium in the

C-D bond in small molecule drugs requires more energy for cleavage by cytochrome P_{450} (CYP_{450}) enzymes as compared to the corresponding C-H bond, a phenomenon known as the Deuterium Kinetic Isotope Effect (Baillie, 1981). Replacing H with D at a C-H bond in a molecule has the potential to attenuate its metabolism if that C-H bond is the site of rate-limiting cleavage by a CYP isozyme. By attenuating metabolism in this manner, area under the curve (AUC), maximum concentration (C_{max}), and half-life may all be increased relative to the non-deuterated molecule (Kushner, et al., 1999).

The presence of D in the C-D bonds of small molecule drugs does not pose a unique safety risk. The C-D bond is more stable than the C-H bond and as such, D is not readily subject to exchange with H in H_2O or in other organic materials (Kushner, et al., 1999). The shape and surface charge of small molecule drugs is defined by the electron cloud of the component atoms. The surface charge and spatial characteristics of deuterated drugs are thought to be biologically indistinguishable from their non-deuterated forms (Di Costanzo, Moulin, Haertlein, Meilleur, & Christianson, 2007; Fisher & Helliwell, 2008). As a consequence, deuterium-substituted small molecule drugs and their non-deuterated forms are not likely to be physiologically different in their binding to macromolecular structures such as receptors, transporters, enzymes, or ion channels.

1.3.1. Clinical Experience with Deuterium

A number of studies in healthy volunteers and patients have evaluated the effects of acute and long-term use of deuterated water (D_2O). Acute exposures of to up to 23% D replacement in plasma were tolerated without reported adverse events (Blagojevic, Storr, & Allen, 1994). In several metabolic labeling studies, healthy subjects consumed daily doses of up to 9.8g D in the form of D_2O for up to 4 to 9 weeks, treatments sufficient to maintain 1.0% to 2.0% D enrichment in body water. No adverse events were reported in these studies (Collins, Eng, Hoh, & Hellerstein, 2003; Kassis & Jones, 2008; Leitch & Jones, 1993; Neese et al., 2002; Strawford, Antelo, Christiansen, & Hellerstein, 2004). Deuterium has also been delivered to humans in the form of D-substituted glucose. Twenty-five subjects with human immunodeficiency virus (HIV) and 10 control subjects were infused intravenously over 48 hours with up to 200 g of [6,6-d2]-glucose, an amount which corresponds to 4.4 g of deuterium. These infusions were not associated with adverse events (Hellerstein et al., 2003).

1.4. SD-809 (Deutetrabenazine)

SD-809 is a deuterated form of tetrabenazine in which the two O-linked methyl groups (CH_3) of the tetrabenazine molecule have been replaced by two trideuteromethyl groups (CD_3). The conversion of SD-809 and tetrabenazine to their respective active metabolites, α-HTBZ and β-HTBZ, proceeds similarly in human liver S9 fraction and in human liver microsomes. The CD_3 groups in SD-809, which are conserved in α-HTBZ and β-HTBZ, attenuate the metabolism of these active metabolites by CYP2D6 relative to the non-deuterated metabolites from tetrabenazine, leading to longer *in vitro* half-lives in human liver microsomes, human liver S9 fraction, and in cells transfected with CYP2D6. These pharmacokinetic benefits have been confirmed in a clinical setting and enable less frequent dosing and reduced the plasma fluctuation of the active metabolites. Furthermore, the attenuated metabolism achieved through deuteration reduces the impact of CYP2D6 genotype on exposure as compared to tetrabenazine with the potential to simplify dosing.

The safety and pharmacokinetics of oral SD-809 have been evaluated in five Phase 1 studies in healthy adult volunteers. Additionally, two Phase 3 studies in adult patients with chorea associated with HD and one Phase 1b study in adolescent patients with tics associated with Tourette syndrome have been completed.

Single doses of SD-809 have been administered to 132 subjects at doses ranging from 7.5 to 25 mg, either alone or in conjunction with CYP2D6 inhibition. Multiple dose regimens of the tablet formulation have also been administered to 24 of those subjects for up to 5 days (at doses up to 22.5 mg twice daily [BID] for 3 days).

For all studies, plasma concentrations of parent drug were low and sporadic because of the rapid and extensive hepatic metabolism of SD-809 to the active metabolites d_6-αHTBZ and d_6-β-HTBZ. Peak plasma concentrations of the active moieties d_6-α-HTBZ and d_6-β-HTBZ were reached within 3 to 4 hours for the tablet formulation without a comparable loss of exposure. In all studies where tetrabenazine was included as a control arm, deuteration was shown to significantly prolong the half-lives of both α - and β-HTBZ, resulting in an increase in exposure (~130% increase) for both active metabolites at comparable doses. Based on the pharmacokinetics over a dose range of 7.5 to 22.5 mg SD-809, it is estimated that a 6-mg dose of SD-809 will provide an exposure ($AUC_{(inf)}$) comparable to 12.5 mg of tetrabenazine. Inhibition of CYP2D6 metabolism by paroxetine administration led to a 3-fold increase in bioavailability of d_6-(α+β)-HTBZ.

In the Phase 1 studies summarized above, no serious adverse events were reported and all adverse events were mild to moderate in intensity. Commonly reported adverse events included headache, somnolence, nausea, dizziness and vessel puncture reaction.

Additional information on the study results may be found in the SD-809 Investigator's Brochure.

2. STUDY OBJECTIVES

The objectives of this study are:

- Evaluate the safety and tolerability of long-term maintenance therapy with SD-809
- Evaluate the efficacy of long-term maintenance therapy of SD-809 to reduce the severity of abnormal involuntary movements of TD
- Evaluate the persistence of the therapeutic effect of SD-809

3. INVESTIGATIONAL PLAN

This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD. Approximately 330 subjects who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other SD-809 study for treatment of moderate to severe TD) will be enrolled. The study will be conducted at approximately 80 centers in the U.S., Europe, and possibly other regions. The study is divided into different parts: Part A and Part B for all countries and an additional Part C for the EU countries. These parts include a Screening Period (Part A), a Titration Period (Part A), a Long-Term Treatment Period (Part A), a Double-Blind, Randomized Withdrawal Period (Part B), treatment after completion of the Randomized Withdrawal Period (Part B), a continued treatment period (Part C), and a Post-Treatment Safety Follow-up Period (Part A, Part B, and Part C).

3.1. Study Design

This is an open-label; single-arm study in which subjects with moderate to severe drug-induced TD who have successfully completed a parent study will be invited to participate. Successful completion of a parent study is defined as (1) study participation through Week 13; (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator; and (3) the subject has no ongoing adverse events that are serious (serious adverse events)[c], severe in intensity, or expected to interfere with their participation in this study.

Informed consent/assent (Part A) will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Subjects who meet the selection criteria will be eligible to participate.

Informed consent/assent for Part B will be obtained after Amendment 06 implementation and before any study procedures related to Part B are performed.

Informed consent/assent for Part C will be obtained after Amendment 07 implementation and before any study procedures related to Part C are performed. Subjects who do not sign the informed consent/assent for Part C will complete the study at Part B Follow-up Call.

Subjects who have successfully completed a parent study may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 evaluation of the parent study. To reduce subject burden, after obtaining informed consent/assent, some data collected in the parent study will be used in the SD-809-C-20 study and will provide some of the baseline data for SD-809-C-20 (see Schedule of Events). In addition to assessments completed for the parent study Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit.

[c] See Section 7 for evaluation of AEs with regard to severity, relationship to study drug, and definition of SAE.

Part A:

Titration Period (up to 6 weeks): As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo titration on SD-809 in this study. During titration, the Investigator, in consultation with the subject (and caregiver, if appropriate), will determine when an adequate level of dyskinesia control has been achieved. The dose of SD-809 should be adjusted (upward or downward) once per week, in increments of 6 mg per day, until there is adequate control of dyskinesia, the subject experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either: a) moderate or severe in intensity or b) meeting the criteria for an serious adverse event), or the maximal allowable dose is reached. If a subject experiences a clinically significant adverse event attributable to SD-809, the Investigator will determine if a dose reduction, dose suspension, or withdrawal from the study is necessary. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2 to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. ***Although subjects will enter the Long-Term Treatment Period after Week 2, titration to optimize dose should occur through Week 6.***

Long-Term Treatment Period (Week 3 until the last dose in Part A): During the Long-Term Treatment Period, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a stable dose by the Week 6 visit may have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at the last dose in Part A (completion of Part A=Week 158 or beginning of Part B after Amendment 06 implementation). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg per day. In the case of the addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, and bupropion), a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. Dose adjustments should be based on all available information, including the subject's and caregiver's reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers.

Subjects who have been on a stable dose of SD-809 and any concomitant DRA for a minimum of 4 weeks will be invited to participate in the Randomized Withdrawal Period (Part B) at the next routine visit at the site after approvals from IRB/Ethics Committee and as required by country regulations. If the subject chooses to participate in Part B, then participation in Part A will end. Subjects who decline to participate in Part B will continue in Part A until Week 158. Subjects who decline participation in Part B will be given an ongoing option to participate at subsequent study visits.

Part B:

Part B will consist of a double-blind; randomized withdrawal period; treatment with SD-809; and post-treatment safety follow-up. The Randomized Withdrawal Period will be 1 week (+3 days

maximum) in duration and will consist of 2 visits, the Pre-withdrawal Visit and the Post-withdrawal Visit. After the Randomized Withdrawal Period, the subjects will resume treatment with SD-809 on the prior established dose for an additional 12 weeks until end of treatment (EOT). A follow-up telephone call will occur 4 weeks after EOT.

At the beginning of the Randomized Withdrawal Period, subjects will be randomized in a blinded fashion to either SD-809 (current dose) or placebo in a 1:1 ratio stratified by concomitant DRA usage. Up to 194 subjects (active subjects as of the approval date of Amendment 06) will be randomized (SD-809 or placebo). Subjects will be required to sign a written informed consent.

Subjects will need to be on a stable dose of SD-809 and any concomitant DRA for a minimum of 4 weeks before starting the Randomized Withdrawal Period.

Subjects will be scheduled to return 1 week (+3 days maximum) after the Pre-withdrawal Visit of the Randomized Withdrawal Period for efficacy and safety assessments.

At the end of this period, subjects will continue treatment with SD-809 at the previous dose administered before the Randomized Withdrawal Period (last dose in Part A). Treatment with SD-809 will continue for 12 weeks until the EOT visit.

Video ratings of the AIMS will occur at the Pre-withdrawal Visit, the Post-withdrawal Visit, and the EOT/early termination (ET) visit.

Part C:

For the EU countries, the study will include a reduced burden safety assessments period (Part C) of 52 weeks for subjects willing to continue in the study and who have completed Part B. Subjects will continue treatment with SD-809 at the current dose administered during the 12-week open-label period of Part B. Subjects will be scheduled to return every 13 weeks (±1 week) until EOT. A follow-up clinic visit will occur 1 week after ET and a follow-up telephone call will occur 4 weeks after EOT/ET.

Post-Treatment Safety Follow-up:

Part A:

Subjects who do not participate in Part B will continue in Part A, discontinue study drug at the Week 158 visit, and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week follow-up-period, subjects should continue to not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage.

Subjects who discontinue study drug in Part A will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

Part B:

Subjects who complete the Randomized Withdrawal Period and subsequent 12 weeks of treatment will complete an EOT visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT.

Subjects who discontinue study drug in Part B will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

Part C:
Subjects who complete the 52 weeks of reduced burden safety assessments period will complete a Part C EOT visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since Part C EOT. Subjects who discontinue study drug in Part C will complete an ET visit, a follow-up clinic visit 1 week later for safety evaluation, and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

3.2. Rationale for Study Design

The study is designed to evaluate the long-term safety and tolerability of SD-809 in subjects with moderate to severe dyskinesia associated with TD (Part A) and the persistence or maintenance of the therapeutic effect of SD-809 in subjects with TD (Part B). Subjects who successfully complete a placebo-controlled efficacy study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 as treatment for moderate to severe TD) will be eligible to enroll. An extension of the study (Part C) with reduced burden safety assessments is added to provide continued therapy for subjects in the EU countries. Part C will be offered only to subjects who completed Part B.
All subjects will have discontinued study drug (SD-809 or placebo) for at least 1 week and consequently will begin dosing at 6 mg BID and titrate to their optimal dose for up to 6 weeks. Although the time to reach an optimal dose will differ among subjects, it is expected that subjects will have reached a pharmacologically active dose by 2 weeks. Accordingly, the long-term period of the study will be deemed to have started after 2 weeks of treatment even though dose adjustment may continue after this point.
The SD-809 dose should be adjusted to identify a dose that reduces dyskinesia and is well tolerated. In addition to the assessments of dyskinesia control and tolerability by the subject, caregiver, and study staff, safety evaluations that target adverse events observed in the drug class (e.g., akathisia) will be employed and considered in the dose-adjustment decision. In this manner, the daily dose of study drug for treating dyskinesia is determined individually for each subject. **Once adequate control of dyskinesia has been achieved, the dose of study drug should not be increased further.** In general, subjects will continue the dose established during titration into the long-term treatment period, but dose adjustments (upward or downward) are permitted so long as they do not occur more often than once per week.
The present investigation is an open-label safety study with a nested, randomized, double-blind, 1-week withdrawal period of SD-809. The study will enroll subjects with TD who were previously exposed to either SD-809 or placebo in a parent study.
The US prescribing information for tetrabenazine indicates that CYP2D6 genotyping should be performed at doses higher than 50 mg, although genotyping is often not performed in clinical practice as the drug is titrated. In the present study, CYP2D6 genotyping will have been performed in a blinded manner in the parent study to allow evaluation of the effect of phenotype on safety parameters at the conclusion of the study.

3.3. Rationale for Dose Selection

As with tetrabenazine, SD-809 treatment will be individualized; therefore, fixed doses will not be evaluated in the study. The starting dose of 6 mg BID of SD-809 provides an AUC of total (α+β)-HTBZ that is comparable to a starting dose of 12.5 mg BID of tetrabenazine, but with a lower peak concentration and reduced plasma fluctuation. Although not approved for the

treatment of TD, there is a substantial body of clinical experience with tetrabenazine in this population. Table 1 provides a summary of 10 published reports describing the use of tetrabenazine in TD.

Table 1: Published Reports Describing the Use of Tetrabenazine in Patients with TD

Publication	Study design	Patients (N)	Dose range (mg/d)	Treatment duration	Responders	Comments
Brandrup, 1961	CR	4	3 pts: 75; 1 pt: ≥150	1.5-3.5 mo	4/4	Marked response in 3/4 patients; 1/4 had somnolence
MacCullum, 1970	CR	2	50	10 mo	2/2	Complete resolution of symptoms; no AEs reported
Godwin-Austen & Clark, 1971	OL; X	6	100	1 wk	5/6	3/6 had complete resolution of symptoms; 2/6 had mild improvement; somnolence reported in 'most' patients
Kazamatsuri, Chien, & Cole, 1972	OL	24	Range: 100-150	4 wk	17/24	13/24 had ≥50% reduction in symptoms; 2/24 withdrew for AEs at doses ≥100 mg/day
Jankovic & Orman, 1988	OL	44	Mean: 97.4 (Range: 25-200)	21 mo (mean)	Mean Score: 2.1*	*Improvement rated 1-5: (1=marked, 2=moderate, 3=fair, 4=poor/none, 5=worse); AEs (N=217): parkinsonism > sedation > depression
Stacy, Cardoso, & Jankovic, 1993	R	78	Not Reported	62 mo (mean)	Mean Score: 3.5†	†Improvement rated 1-4 (1=mild; 2=mod,; 3=mod with function benefit; 4=marked)
Jankovic & Beach, 1997	R	94	Mean: 97 (Range: 25-400)	35 mo (mean)	87/94	Responders had marked or moderate improvement. Most common AEs: somnolence > parkinsonism > depression > insomnia
Ondo, et al., 1999	OL	20	Mean: 57.9 (Range: 25-150)	20 wk (mean)	Mean reduction of 9.7 points in AIMS motor score	1/20 patients withdrew for somnolence (somnolence in 5/20, parkinsonism in 5/20)
Jankovic, Hunter, Mejia, & Vuong, 2004	R	139	Mean: 56.6 (Range: 6.25–200)	30 mo (mean)	116/139	Had marked or moderate improvement Parkinsonism (27.5%), drowsiness or fatigue (24.2%), akathisia (10.1%)
Paleacu et al., 2004	R	15	Range: 25-150	22 mo (mean)	10/15+	+7/15 with moderate/marked improvement

Abbreviations: AE, adverse event; AIMS, Abnormal Involuntary Movement Scale; CR, case report; mo, month; OL, open-label study; pt, patient; R, retrospective review; X, crossover study; wk, week.

Treatment durations of over 5 years (Stacy, et al., 1993) and daily doses of up to 400 mg/day (Jankovic & Beach, 1997) have been reported with tetrabenazine. Starting doses varied across studies, but several authors reported initiating treatment at 12.5 mg BID and titrating based on symptom control and tolerability (Jankovic & Beach, 1997; Ondo, et al., 1999; Paleacu, et al., 2004). In addition, a mean dose of approximately 100 mg per day was frequently reported in these studies and was associated with a high response rate and an acceptable adverse event

profile. The frequencies and types of adverse events observed in the TD population have generally been similar to those described in the HD population.

Based on the available published literature for tetrabenazine, and the comparability of 6 mg of SD-809 with 12.5 mg of tetrabenazine with regard to plasma AUCs, initiating treatment with SD-809 at 6 mg BID and titrating to a total daily dose of 48 mg per day (comparable in AUC to 100 mg of tetrabenazine) is considered to be appropriate for the present study.

In the present study, the dose level of SD-809 treatment will be evaluated on a weekly basis during the dose adjustment or Titration Period, based on assessments of dyskinesia control and adverse events, in order to determine if dose adjustment is needed. This approach is consistent with the tetrabenazine prescribing information for the treatment of chorea associated with HD. Weekly dose adjustments for insufficient dyskinesia control should occur in increments of 6-mg changes in the total daily dose. Dose reductions greater than 6 mg should be reviewed with the Medical Monitor (see Section 5.2.4).

In a population pharmacokinetics (PPK) analysis from Study SD-809-C-18, for patients ≥100 kg with functional CYP2D6 status, 60 mg/day given in 2 divided doses resulted in similar total (α+β)-HTBZ to that in healthy subjects administered 24 mg BID. For lower body weight patients (i.e., those <100 kg) with functional CYP2D6 status, a 48 mg/day dose was identified as resulting in similar total (α+β)-HTBZ exposure compared to healthy subjects administered 24 mg BID. Based on these simulations, dosing in the current study will be based on baseline body weight (<100 kg and ≥100 kg) and CYP2D6 impairment status at baseline (i.e., impaired [receiving a strong CYP2D6 inhibitor or is a CYP2D6 poor metabolizer] or not impaired) (see Appendix 13 for details).

For subjects with a body weight less than 100 kg, the maximum total daily dose of SD-809 is 48 mg/day (24 mg BID), unless the subject is receiving a strong CYP2D6 inhibitor (e.g., paroxetine; see Appendix 13), in which case the maximum total daily dose is 36 mg/day. For subjects with a body weight of 100 kg or more, the maximum total daily dose of SD-809 is 60 mg/day (30 mg BID), unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 42 mg/day.

4. STUDY POPULATION

4.1. Population Characteristics

Male and female adult subjects with TD who have successfully completed the parent efficacy study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for treatment of moderate to severe TD) and meet eligibility criteria will be enrolled.

4.2. Inclusion Criteria

1. Subject is at least 18 years of age at Screening.
2. Subject has successfully completed[d] Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for treatment of moderate to severe TD.
3. Subject has a history of using a DRA for at least 3 months (or 1 month in subjects 60 years of age and older). See Appendix 15.
4. Subject has a clinical diagnosis of TD and has had symptoms for at least 3 months prior to Screening.
5. For subjects with underlying psychiatric illness:
   - Subject is psychiatrically stable and has had no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before Screening (45 days for antidepressants).
   - Subjects on long acting (depot) medications have been on stable therapy (dose, frequency) ≥3 months before Screening.
   - Subject has a health care provider who is aware of the subject's participation in the trial, and does not anticipate any changes in the subject's treatment regimen (drug, dose, frequency) in the next 3 months.
6. Subject has a history of being compliant with prescribed medications.
7. Subject is able to swallow study drug whole.
8. Subject has provided written, informed consent or, if subject lacks the capacity to provide informed consent, a legally authorized representative (LAR) has provided written informed consent and the subject has provided assent.
9. In the opinion of the Investigator, the subject lives in a stable environment and has adequate supervision when necessary to comply with all study procedures, attend all study visits, and safely participate in the trial.
10. Subject has sufficient reading skills to comprehend the subject-completed rating scales.
11. Female subjects of childbearing potential[e] agree to use one of the following acceptable methods of contraception from Screening through study completion if sexually active:
    - IUD or intrauterine system in place for at least 3 months prior to screening;

[d] Successful completion is defined as (1) study participation through Week 13, (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator, and (3) the subject has no ongoing AEs that are serious or severe in intensity or are expected to interfere with safety evaluations in this study.

[e] Non-childbearing potential for females is defined as postmenopausal (amenorrheic for at least 1 year and serum follicle stimulating hormone (FSH) level consistent with postmenopausal status), or a documented hysterectomy; bilateral oophorectomy; or bilateral tubal ligation ≥6 months prior to study initiation.

- Subject or partner using barrier method (e.g., condom, diaphragm, or cervical cap) with spermicide from Screening through study completion;
- Partner has a documented vasectomy >6 months prior to enrollment;
- Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to Screening.

4.3. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded:

1. Subject has received tetrabenazine within 7 days of Baseline.
2. Subject has received any of the following medications within 30 days of Baseline:
   - Reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Baseline), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
   - Metoclopramide, promethazine, and prochlorperazine
   - Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc.), or monoamine oxidase inhibitors (MAOIs)
   - Levodopa or dopamine agonists
3. Subject has a neurological condition other than TD that may interfere with assessing the severity of dyskinesias.
4. Subject has a serious untreated or undertreated psychiatric illness at Baseline.
5. Subject has active suicidal ideation at Baseline.
6. Subject has a history of any of the following within 6 months of Baseline:
   - Previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence at the time of suicidal thought
   - Previous preparatory acts to commit suicide or suicidal behavior
   - A previous actual, interrupted, or aborted suicide attempt
7. Subject has a score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at Baseline.
8. Subject is developmentally disabled or has evidence of dementia.
9. Subject has an unstable or serious medical illness at Baseline.
10. Subject has history (within 3 months) or presence of violent behavior.
11. Subject has a Fridericia-corrected QT interval (QTcF) value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block [RBBB]) on 12-lead electrocardiogram (ECG) at Baseline.
12. Subject has evidence of hepatic impairment at Screening of the parent study, as indicated by:
    - Aspartate transaminase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)
    - Alkaline phosphatase (ALP) or total bilirubin (TBil) >2 times the ULN
      - Note: Subjects with Gilbert's Syndrome are eligible to participate if approved by the Medical Monitor.
      - Note: Subjects with abnormalities in two or more of these analytes (AST, ALT, ALP, TBil) must be approved by the Medical Monitor to be enrolled.
    - Prothrombin time >17 seconds (i.e., prothrombin time prolonged >4 seconds over the ULN
    - Positive hepatitis B surface antigen (HBsAg)

13. Subject has evidence of significant renal impairment at Screening of the parent study, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockroft-Gault formula.
14. Subject has known allergy to tetrabenazine or to any of the components of study drug.
15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18, Study SD-809-C-23, or any other eligible SD-809 parent study) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer.
16. Subject is pregnant or breastfeeding at Baseline.
17. Subject acknowledges present use of illicit drugs at Screening.
18. Subject has a history of alcohol or substance abuse in the previous 12 months, as defined in the DSM-V, or subject is unable to refrain from substance abuse throughout the study.

5. STUDY TREATMENT

The study drug to be used in this trial is a tablet formulation of SD-809. Five dosage strengths of SD-809 will be available for use: 6, 9, 12, 15, and 18 mg tablets. The actual dose of SD-809 received by the subject will be determined by the clinical pack supplied. The initial drug supply will be provided to the subject in the clinic at the Baseline visit.

5.1. Study Drug

5.1.1. SD-809

The study drug is a matrix formulation in the form of a tablet to be administered with food. Study drug is coated with a polymer coating to aid in swallowing. SD-809 tablets have been manufactured according to current Good Manufacturing Practices regulations.

During titration/dose adjustment in Part A, SD-809 tablets will be labeled according to applicable regulatory guidelines and supplied in weekly blister packs as 6, 9, 12, 15, and/or 18 mg tablets. Each blister pack will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies. **During long-term treatment, SD-809 will be supplied in 30-count bottles and labeled according to applicable regulatory guidelines.** During the 1-week double-blinded Randomized Withdrawal Period, SD-809 will be supplied in 20-count bottles and labeled according to the applicable regulatory guidelines.

During Part C, SD-809 will be supplied in 30-count bottles.

Complete details regarding SD-809 supply, dispensing, and ordering will be provided in the study Operations Manual.

SD-809 tablets must be stored in a secure area with access limited to authorized staff, protected from light at controlled room temperature, 15°C to 25°C (59°F to 77°F).

5.1.2. Placebo (Part B: Double-Blind, Randomized Withdrawal Period Only)

Placebo tablets are identical in appearance to the SD-809 and contain the same inactive ingredients as SD-809.

5.2. Treatment Regimen

5.2.1. General Guidelines

The following general guidance applies to treatment regimens for all subjects in the study:

- All treatment regimens will be administered BID with meals, approximately 10 hours apart during the day.
- The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the parent study. Prior treatment assignment from the parent study will remain blinded.

- For subjects with body weight less than100 kg, the maximum total daily dose of SD-809 is 48 mg/day (24 mg BID), unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 36 mg/day. For subjects with body weight 100 kg or more, the maximum total daily dose of SD-809 is 60 mg/day (30 mg BID), unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 42 mg/day.

Table 2: Maximum Daily Dose Level During the Maintenance Period

Body weight (kg)*	**Target dose (schedule)**	
	Not CYP2D6 impaired	**On strong CYP2D6 inhibitor**
<100 kg	48 mg/day (24 mg BID)	36 mg/day (18 mg BID)
≥100 kg	60 mg/day (30 mg BID)	42 mg/day (21 mg BID)

*Body weight at the time of dose increase >48 mg/day

- Daily doses will be administered according to instructions provided in the Pharmacy Manual.
- During the titration period, the dose of SD-809 should be increased on a weekly basis in increments of 6 mg of the total daily dose until:
  - There is adequate control of dyskinesia;
  - The subject experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meets the criteria for a serious adverse event); or
  - The maximal allowable dose is reached.
- Study drug will be titrated over the initial 6 weeks of therapy, if necessary, to identify a dose that provides adequate dyskinesia control and is well tolerated. Changes in dose should not be made more often than once per week unless the subject is experiencing an intolerable adverse event.
- If a subject experiences a clinically significant adverse event attributable to SD-809, the Investigator will determine if a dose reduction or dose suspension, or withdrawal from the study is necessary.

Once adequate control of dyskinesia has been achieved, the dose of study drug should not be increased further.

5.2.2. Dosing in Long-Term Treatment (Week 3 Until the Last Dose in Part A)

Initially during the Long-Term Treatment Period, a well-tolerated dose of SD-809 that provides adequate dyskinesia control may not yet be established. Dose adjustments should continue during long-term treatment as specified in Section 5.2.1. Once a stable dose is achieved, SD-809 should be dosed at the same level throughout the remaining Long-Term Treatment Period. If necessary, however, the dose may be adjusted further (upward or downward) to optimize dyskinesia control or minimize adverse events. In general, dose changes are limited to 6 mg of the total daily dose (see Section 5.2.4). However, such changes in dose should not occur more frequently than once per week.

Once subjects are on a stable dose of SD-809, drug will be provided to study subjects in 30-count bottles until the next specified visit. Each order will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies.

5.2.3. Dosing in the Double-Blind, Randomized Withdrawal Period

Subjects in the Randomized Withdrawal Period will continue to receive their current dose of SD-809 or will receive matching placebo. At the end of the Randomized Withdrawal Period, subjects will continue with, or return to, the same dose of SD-809 taken before the Randomized Withdrawal Period (last dose in Part A), beginning the day after the Post-withdrawal Visit and continuing for 12 weeks. Subjects who do not return for the Post-withdrawal Visit within the 10 days (1 week [+3 days maximum]) may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary) per the guidelines in Table 3. Titration is not permitted during the Randomized Withdrawal Period and will be allowed after return to open-label dosing.

Table 3: Titration Schedule After 1-Week Randomized Withdrawal Period (if Necessary)

1 Week blinded daily dose	1 Week SD-809 titration daily dose (Step 1)	1 Week SD-809 titration daily dose (Step 2)	SD-809 daily dose after completing titration
12 mg or placebo	N/A	N/A	12 mg
18 mg or placebo	12 mg	N/A	18 mg
24 mg or placebo	12 mg	N/A	24 mg
30 mg or placebo	18 mg	24 mg	30 mg
36 mg or placebo	18 mg	24 mg	36 mg
42 mg or placebo	24 mg	30 mg	42 mg
48 mg or placebo	24 mg	36 mg	48 mg
54 mg or placebo	30 mg	42 mg	54 mg
60 mg or placebo	30 mg	48 mg	60 mg

Abbreviation: N/A, not applicable.

5.2.4. Dosing in Part C

The drug will be provided to study subjects in 30-count bottles. Each order will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations.

Subjects who do not return for Part C Visit 1 within 10 days of completing the Part B EOT Visit may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary) per the guidelines in Table 4 .

Table 4: Titration Schedule Part C End of Treatment Period (if Necessary)

Part B open-label period daily dose	1 week SD-809 titration daily dose (Step 1)	1 week SD-809 titration daily dose (Step 2)	SD-809 daily dose after completing titration
12 mg or placebo	N/A	N/A	12 mg
18 mg or placebo	12 mg	N/A	18 mg
24 mg or placebo	12 mg	N/A	24 mg
30 mg or placebo	18 mg	24 mg	30 mg

Table 4: Titration Schedule Part C End of Treatment Period (if Necessary) (Continued)

Part B open-label period daily dose	1 week SD-809 titration daily dose (Step 1)	1 week SD-809 titration daily dose (Step 2)	SD-809 daily dose after completing titration
36 mg or placebo	18 mg	24 mg	36 mg
42 mg or placebo	24 mg	30 mg	42 mg
48 mg or placebo	24 mg	36 mg	48 mg
54 mg or placebo	30 mg	42 mg	54 mg
60 mg or placebo	30 mg	48 mg	60 mg

Abbreviation: N/A, not applicable.

5.2.5. Dose Reduction, Suspension, or Discontinuation

If a subject experiences a clinically significant adverse event (see Section 7) that is attributed to SD-809, the Investigator will use his or her judgment to determine if a dose reduction, dose suspension, or withdrawal from the study is necessary. Dose adjustments should be made based on all available information including the subject's and caregiver's reports of adverse events and dyskinesia control, the clinical assessment of safety and efficacy by the Investigator and information from rating scales.

Dose Reduction

Dose reduction should generally occur in increments of 6 mg/day, except in the case of addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, bupropion), in which case a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. A dose reduction of 6 mg/day can be made by requesting that the next lowest dose level be assigned through the Interactive Response Technology system. Dose reductions greater than 6 mg/day should be reviewed with the Medical Monitor. If a subject requires a dose reduction based on a telephone contact during the Long-Term Treatment Period, an unscheduled clinic visit should be conducted in a timely manner thereafter.

Suspension

Suspension of study drug for up to 1 week, if warranted, is allowed.

Suspensions of study drug for adverse events must be reviewed with the Medical Monitor before therapy is restarted. If study drug is restarted after a suspension for an adverse event, a dose reduction of 6 mg or more is permitted.

If a subject's serum potassium or magnesium falls below the lower limit of normal, study drug must be suspended. The Medical Monitor must be contacted to determine the appropriate investigation and treatment. SD-809 may only be restarted once serum potassium or magnesium have normalized.

Suspensions for more than 7 days must be reviewed by the Medical Monitor. If the subject restarts study drug within 7 days of suspension, the full dose of SD-809 may be resumed without titration. If subject restarts study drug greater than 7 days following a suspension, re-titration will be required. Dose re-titrations will necessitate additional unscheduled visits and telephone contacts which will be needed to ensure that the subject reaches the appropriate maintenance dose safely and without undue delay, and to ensure adherence to the treatment regimen and retention of any unused drug materials.

Discontinuation

Discontinue study drug and complete an ET visit if, based on Investigator evaluation of readings of 12-lead ECGs, the subject meets either of the following criteria:

- a mean[f] QTcF value >500 msec or
- a mean[gf] change in QTcF of >60 msec from Baseline

The reason for a dose reduction, suspension, or discontinuation must be clearly documented.

5.3. Treatment Administration

Each tablet should be swallowed whole with water and not broken, crushed, or chewed. Tablets should be taken with food and not be taken on an empty stomach.

Subjects should be instructed to take the study drug with meals: tablets will be administered BID with meals in the morning and evening, as indicated on drug packaging. It is recommended that BID doses be taken approximately 10 hours apart during the day. A minimum of 6 hours should elapse between doses. If a subject misses a dose and it is within 6 hours of their next dose, the missed dose should be skipped.

5.4. Accountability of Study Drug

The study drug must be used in accordance with the protocol and only under the direction of the Investigator. All materials supplied are for use only in this clinical study and should not be used for any other purpose.

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received, dispensed, and disposition of unused study drug.

A drug dispensing log must be kept current and will contain the following information:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject.

Prior to the Pre-withdrawal Visit and Post-withdrawal Visit, the Investigator or designated site staff must place a call to remind the subject to bring all remaining study drugs to the visit. The Investigator or designated site staff must collect the study drug(s) from the subject and conduct drug accountability.

The inventory must be available for inspection by the Sponsor and/or study monitor during the study. Drug supplies, including partially used or empty containers, will be fully accounted for at the end of the study by the study monitor. Records of final disposition of the study drug shall be maintained by the Investigator. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the study drug. Such records must be submitted to the Sponsor.

[f] Mean value is calculated based on three 12-lead ECGs interpreted in the central ECG laboratory (Section 6.7.1). Patients with a ventricular pacemaker will be reviewed by the Medical Monitor.

5.5. Study Drug Compliance

The Investigator or designated study staff is responsible for monitoring the subject's compliance with study drug during the trial. Compliance will be assessed by tablet count, i.e., evaluation of returned study drug blister cards/bottles (e.g., amount used/amount expected to be used in interval between visits) and must be reviewed at every visit while the subject is still in clinic to determine if the subject is taking study drug as directed.

Compliance will be evaluated by calculating the number of tablets used (tablets dispensed minus tablets returned) divided by the expected number of tablets to be used. A subject will be deemed compliant over the overall treatment period if the subject has taken 80% to 105% of the expected tablets of study drug.

6. STUDY METHODS AND PROCEDURES

6.1. Screening Period

6.1.1. Prior Data from Subject's Parent Study

See Schedule of Events for data to be imported from the parent study after informed consent/assent.

Subjects who have successfully completed a parent study may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 (visit window up to 10 days) evaluation of the parent study. To reduce subject burden, after obtaining informed consent/assent, some data collected in the parent study will be used in the SD-809-C-20 study and provide some of the baseline data for SD-809-C-20 (see Schedule of Events). In addition to assessments completed for the parent study Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit. All subjects participating in SD-809-C-20 are expected to rollover to SD-809-C-20 at the Week 13 visit of the parent study.

Baseline visit study drug will be shipped after site's approval to receive study drug. See Operations Manual for further details.

6.1.2. Baseline Visit (Day 0)

See the Schedule of Events for a detailed summary of activities.

Subjects will return to the clinic on Day 0 to undergo baseline evaluation. Subjects who continue to meet selection criteria will be enrolled in the study.

Prior to conduct of any study-specific screening procedures, the Investigator or designee will explain to the subject (and caregiver, if applicable) the study procedures, including the risks involved and the fact that their participation is voluntary. If subject lacks the capacity to provide informed consent, a legally authorized representative must provide written informed consent and the subject must provide assent. Each subject (and caregiver, if applicable) will acknowledge receipt of this information by signing and dating a current, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent, or subject assent if an LAR is utilized, for their involvement in the study in the presence of the Investigator, or designee, who will also sign and date the informed consent or assent.

The Baseline clinic visit will consist of the following:

- Obtain or verify informed consent or assent (for subjects who do not have a legally authorized representative)
- Update medical history
- Urine pregnancy test (women of child-bearing potential only)
- AIMS
- Video recording of AIMS (see Section 6.8.1)
- 12-lead ECG
- Montreal Cognitive Assessment (MoCA©)
- Modified Craniocervical Dystonia Questionnaire (CDQ-24)
- Baseline results will be assessed by the Investigator or Sub-Investigator, and subjects who meet eligibility criteria will be enrolled into the study.

- Subjects will be provided with 1 week of study drug
- Week 1 telephone visit will be scheduled

6.2. Dose Adjustment/Titration Period

All subjects will interact weekly with the clinical site, either by telephone contact or clinic visit, during the dose adjustment/titration period, to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. Safety evaluations include laboratory testing, ECGs, monitoring for adverse events and rating scales for motor function, depression, cognitive function, akathisia, and somnolence.

As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week after completion of the parent study, they will undergo titration on SD-809 in this study. During titration, the Investigator, in consultation with the subject (and caregiver, if applicable), will determine when an adequate level of dyskinesia control has been achieved. The dose of SD-809 should be adjusted on a weekly basis (upward or downward), in increments of 6 mg of total daily dose, until there is adequate control of dyskinesia; the subject experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meets the criteria for a serious adverse event); or the maximal allowable dose is reached. If a subject experiences a clinically significant adverse event attributable to SD-809, the Investigator will determine if a dose reduction or suspension is necessary. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2 to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. Although subjects will enter the Long-Term Treatment Period after Week 2, titration may occur through Week 6 to optimize dose.

Once adequate control of dyskinesia has been achieved, the dose of SD-809 should not be increased further.

If a subject experiences an adverse event that is attributed to study drug, the Investigator will use his or her judgment to determine if a dose reduction or suspension is necessary. Dose adjustments should be made based on all available information including the subject's (and caregiver's, if applicable) reports of adverse events and dyskinesia control, the clinical assessment of safety and efficacy by the Investigator, and information from rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS), the Barnes Akathisia Rating Scale (BARS), the HADS, the Columbia Suicide Severity Rating Scale (C-SSRS), the Epworth Sleepiness Scale (ESS), and the MoCA©. At the end of the dose adjustment/titration period, the subject's dose will be established for the remainder of the Long-Term Treatment Period.

6.2.1. Weeks 1 and 2

See the Schedule of Events for a detailed summary of activities.

Telephone contact will be scheduled at Week 1 and a clinic visit at Week 2 of the study for evaluation of safety and SD-809 dose.

The **Week 1 (±1 day) telephone contact** will include the following activities:

- Assessment of adverse events, dyskinesia control (in consultation with the caregiver, if applicable), and concomitant medication use
- Evaluation of study drug dose and adjustment, if necessary
- Re-order study drug
- Next clinic visit will be scheduled/reconfirmed

The **Week 2 (±3 day) clinic visit** will include the following activities:

- Assessment of adverse events, dyskinesia control (in consultation with the caregiver, if applicable), and concomitant medication use
- Vital signs
- Weight
- 12-lead ECG
- AIMS
- UPDRS Part III (motor examination)
- BARS
- HADS
- C-SSRS: Since Last Visit version
- ESS
- Assessment of study drug accountability/compliance
- Evaluation of SD-809 dose level and adjustment, if necessary, based on subject's reports of adverse events and dyskinesia control (in consultation with the subject and caregiver, if applicable), clinical assessment of safety and efficacy, and information from the above rating scales.
- Re-order study drug (See Operations Manual for further details)
- The next telephone contact will be scheduled/reconfirmed.

6.3. Long-Term Treatment Period (Week 3 Until the Last Dose in Part A)

All subjects will enter the Long-Term Treatment Period after Week 2, although dose adjustment should continue through Week 6. During titration, all subjects will be contacted by telephone at Weeks 3 and 5 and will return to the clinic at Weeks 4 and 6 for evaluation of safety and dyskinesia control and blood sampling for safety labs (Week 6 only). **Subjects who have not achieved a dose that adequately controls dyskinesia and is well tolerated by the Week 6 clinic visit should have unscheduled visits or telephone contacts to further adjust their dose upward or downward.** Site interactions for dose adjustment should alternate between telephone contacts and clinic visits.

During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at the last dose in Part A (completion of Part A=Week 158 or beginning of enter Part B after Amendment 06 implementation). Further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg. Dose adjustments should be based on all available information, including the subject's (and caregiver's, if applicable) reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers. At Weeks 28, 54, 106, and 158, subjects will undergo a more comprehensive evaluation, including physical examination, complete neurological examination (Weeks 54, 106, and 158 only), safety labs, 12-lead ECG, urine pregnancy test for women of childbearing potential, and performance of all rating scales.

6.3.1. Telephone Contacts (Week 3 ± 3 Days and Week 5 ± 3 Days)

See the Schedule of Events for a detailed summary of activities.

Telephone contacts will be scheduled during Weeks 3 and 5 to assess adverse events, dyskinesia control (in consultation with the caregiver, if applicable), concomitant medication use, evaluation of study drug dose level and adjustment, if necessary, and to schedule/confirm the next visit. Following the above assessments, study drug will be re-ordered according to specified procedures.

6.3.2. Clinic Visits (Weeks 4, 6, 15, 41, 67, 80, 93, 106, 119, 132, and 145 [All ± 3 Days])

See the Schedule of Events for a detailed summary of activities.

Long-Term Treatment Period clinic visits include the following activities:

- Assessment of adverse events, dyskinesia control (in consultation with the caregiver, if applicable), and concomitant medication use
- Weight
- Vital signs (at Week 6, include orthostatic blood pressure and pulse)
- 12-lead ECG (Weeks 4, 6, and 41)
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis (Week 6 only)
- AIMS
- Video recording of AIMS (Weeks 6, 15, and 41)
- UPDRS Part III (motor examination)
- BARS
- HADS
- C-SSRS: Since Last Visit version
- ESS (excluding at weeks 119 and 145)
- Clinical Global Impression of Change (CGIC)
- PGIC
- MoCA© (Weeks 6, 15, 41, 67, 80, 93, and 132)
- Modified CDQ-24 (Weeks 6, 15, and 41)
- Assessment of study drug accountability/compliance
- Evaluation of study drug dose level and adjustment, if necessary (through Week 6)
- Re-order study drug (see Operations Manual for further details)
- Next clinic visit and/or telephone contact will be scheduled/reconfirmed

Subjects should continue to receive their long-term treatment dose after the Week 6 clinic visit, although further dose adjustments are permitted if clinically indicated.

6.3.3. Clinic Visits (Part A) (Weeks 28, 54, 106 and 158 [All ± 3 Days] or Early Termination)

See the Schedule of Events for a detailed summary of activities.

At Weeks 28, 54, 106, 158, or the ET visit, subjects will undergo a more comprehensive evaluation, including:

- Assessment of adverse events, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use
- Physical examination (brief physical examination only at Week 28), vital signs (including orthostatic blood pressure and pulse at Weeks 54, 106, and 158/ET), and weight
- Complete neurological examination (Weeks 54, 106, and 158/ET only)

- Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (women of childbearing potential only)
- 12-lead ECG
- AIMS
- Video recording of AIMS
- UPDRS Part III (motor examination)
- BARS
- HADS
- C-SSRS: Since Last Visit version
- ESS
- CGIC
- PGIC
- MoCA©
- Modified CDQ-24
- Assessment of study drug accountability/compliance and collection of all study drug
- Re-order study drug (see Operations Manual for further details, Weeks 28 and 54 only)
- The next clinic visit will be scheduled/reconfirmed

Unless a subject discontinues the study early or opts to participate in Part B, treatment with study drug will stop at the Week 158 visit.

Note: If the subject discontinues from the study early, every effort should be made to complete the ET procedures as outlined above and in the Schedule of Events. In addition, subjects discontinuing prematurely from the study should have a follow-up visit 1 week after discontinuing therapy and a follow-up telephone contact 4 weeks after discontinuing therapy, if possible. The procedures outlined in Section 6.6 should be followed.

6.4. Double-Blind, Randomized Withdrawal Period (Part B)

See the Schedule of Events for a detailed summary of activities.

At the Pre-withdrawal Visit and Post-withdrawal Visit (1 week [+3 days maximum] from the Pre-withdrawal Visit), the following activities should be performed:

- Obtain or verify informed consent or assent (for subjects who do not have a legally authorized representative) after Amendment 06 implementation (Pre-withdrawal Visit only).
- Randomize subject via Interactive Response Technology (IRT), and dispense study drug (Pre-withdrawal Visit only)
- Assessment of adverse events, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use
- Vital signs (Pre-withdrawal Visit to include orthostatic blood pressure and pulse) and weight
- Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (Pre-withdrawal Visit only; women of childbearing potential only)
- Single pharmacokinetic (PK) blood sample (Post-withdrawal Visit only)
- 12-lead ECG
- AIMS
- Video recording of AIMS
- UPDRS Part III (motor examination)
- BARS
- HADS

- C-SSRS: Since Last Visit version
- ESS
- MoCA©
- Assessment of study drug accountability/compliance and collection of all study drug before randomization into the Randomized Withdrawal Period and at the end of the Randomization Withdrawal Period
- Subjects will be provided with a sufficient supply of study drug (blinded at Pre-withdrawal Visit)
- The next clinic visit will be scheduled/reconfirmed.

Clinic Visits (Part B Open-label Treatment) End of Treatment or Early Termination
See the Schedule of Events for a detailed summary of activities.
At the Part B EOT or Part B ET visit, subjects will undergo a more comprehensive evaluation, including:

- Assessment of adverse events, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use
- Physical examination, vital signs (including orthostatic blood pressure and pulse), and weight
- Complete neurological examination
- Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (women of childbearing potential only)
- 12-lead ECG
- AIMS
- Video recording of AIMS
- UPDRS Part III (motor examination)
- BARS
- HADS
- C-SSRS: Since Last Visit version
- ESS
- MoCA©
- Assessment of study drug accountability/compliance and collection of all study drug
- The next clinic visit will be scheduled/reconfirmed.

Unless a subject discontinues the study early, treatment with study drug will stop at the EOT visit.
Note: If the subject discontinues from the study early, every effort should be made to complete the ET procedures as outlined above and in the Schedule of Events. In addition, subjects discontinuing prematurely from the study should have a follow-up visit 1 week after discontinuing therapy and a follow-up telephone contact 4 weeks after discontinuing therapy, if possible. The procedures outlined in Section 6.6 should be followed.

6.5. Reduced Burden Safety Assessments (Part C)

See the Schedule of Events for a detailed summary of activities.
At Part C Visit 1, the subjects will undergo the activities performed at the Part B EOT visit as described above and will sign the informed consent/assent for Part C.
At Part C Visit 2, Visit 3, Visit 4, or the EOT/ET Visit, subjects will undergo reduced burden safety assessments, including:

- Physical examination, vital signs (including resting blood pressure and pulse), and weight
- Complete neurological examination (Part C EOT/ET only)
- Urine pregnancy test (done locally at the study site)
- 12-lead ECG
- C-SSRS: Since Last Visit version
- Assessment of study drug accountability/compliance and collection of all study drug
- Assessment of AEs and concomitant meds
- Re-order study drug (see Operations Manual for further details, Part C Visit 2, Visit 3, and Visit 4)
- The next clinic visit will be scheduled/reconfirmed

Treatment with study drug will stop at the Part C EOT Visit.

6.6. Post-Treatment Safety Follow-up

Following discontinuation of study drug at the Week 158 visit in Part A, subjects will have a clinic visit at Week 159 for evaluation of safety, dyskinesia, and motor function and a telephone contact at Week 162 for review of adverse events and concomitant medication use since Week 159.

Following discontinuation of study drug at the ET visit in Part A, subjects will have a clinic visit 1 week later for evaluation of safety, dyskinesia, and motor function and a telephone contact 4 weeks after the last dose for review of adverse events and concomitant medication use since ET.

Following discontinuation of study drug at the EOT visit in Part B, subjects will have a telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT, unless they will continue with Part C.

Following discontinuation of study drug at the ET visit in Part B, subjects will have a clinic visit 1 week later for evaluation of safety, dyskinesia, and motor function and a telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

During the first week after stopping study drug, subjects should not take prohibited concomitant medications. Between the Week 158, EOT, or ET visit and the follow-up telephone contact, concomitant medication use is per the discretion of the Investigator.

Subjects in Part C who complete the 52 weeks of reduced burden safety assessments period will complete a Part C EOT Visit and a follow-up telephone contact 4 weeks after the last dose of study drug, to evaluate the adverse events and concomitant medication use since Part C EOT.

Subjects who discontinue study drug in Part C will complete an ET visit, a follow-up clinic visit 1 week later for safety evaluation, and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

6.6.1. Clinic Visit (Week 159 ±3 Days or 1 Week after Early Termination ±3 Days)

See the Schedule of Events for a detailed summary of activities.

All subjects will return 1 week after Week 158 (Part A) or the ET visit (Part A or Part B) for evaluation of safety, dyskinesia, and motor function. The following activities should be performed:

- Assessment of adverse events, dyskinesia control (in consultation with the caregiver, if appropriate), and concomitant medication use
- Vital signs

- Weight
- AIMS
- UPDRS Part III (motor examination)
- BARS
- HADS
- C-SSRS: Since Last Visit version
- ESS
- Next telephone contact will be scheduled/reconfirmed

All subjects will return 1 week after the ET visit (Part C) for evaluation of safety. The following activities should be performed:

- Assessment of adverse events and concomitant medication use
- Vital signs
- Weight
- C-SSRS: Since Last Visit version
- Next telephone contact will be scheduled/reconfirmed

6.6.2. Telephone Contact (4 Weeks After EOT/ET ± 3 Days)

All subjects will have a follow-up telephone contact (4 weeks after their last dose of study drug [Week 158]) (Part A); or 4 weeks after the EOT visit (Part B); or 4 weeks after the ET visit (Part A or Part B). During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about adverse events and concomitant medication use since the subject's last evaluation.

In Part C, all subjects will have a follow-up telephone contact 4 weeks after EOT/ET Visit (±3 days). During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about adverse events and concomitant medication use since the subject's last evaluation.

6.7. Unscheduled Visit(s)

See the Schedule of Events for a detailed summary of activities.

For unscheduled clinic visit(s) needed during Part A and Part B, the following activities should be performed, if indicated:

- Assessment of adverse events, dyskinesia control (in consultation with the subject and caregiver), and concomitant medications
- Vital signs and weight
- 12-lead ECG at the Investigator's discretion
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis (at the Investigator's discretion)
- Single pharmacokinetic (PK) blood sample (for Unscheduled Visits due to serious adverse event, within 48 hours, if possible)
- UPDRS Part III (motor examination) (at the Investigator's discretion)
- BARS (at the Investigator's discretion)
- HADS
- C-SSRS: Since Last Visit version

- ESS (at the Investigator's discretion)
- Evaluation of study drug dose level and adjustment, if necessary (at the Investigator's discretion)
- Re-order study drug (at the Investigator's discretion)

For unscheduled clinic visit(s) needed during Part C, the following activities should be performed, if indicated:

- Vital signs and weight
- 12-lead ECG at the Investigator's discretion
- C-SSRS: Since Last Visit version
- Dispense study drug (at the Investigator discretion)
- Assess AEs

6.7.1. Unscheduled Visit(s) for Change in Antipsychotic Regimen

Subjects undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring. In such cases, the Investigator should contact the Medical Monitor to review these procedures.

- Subjects undergoing such a change in **oral** antipsychotic treatment should have an unscheduled visit between 1-2 weeks thereafter.
- Subjects undergoing an increase in dose of a **long-acting injectable** (LAI) antipsychotic, switching to an LAI treatment, or having an additional LAI antipsychotic treatment added to their regimen should have an unscheduled visit within the following timeframe, based on the prescribed LAI antipsychotic:
    - 4-5 weeks: fluphenazine decanoate
    - 8-9 weeks: risperidone LA, haloperidol decanoate, olanzapine pamoate, Zuclopenthixol decanoate
    - 12-13 weeks: all other LAI antipsychotics

On the morning of the clinic visit, the subject should hold their SD-809 dose until they are in the clinic. Upon reaching the clinic, the following activities should be performed:

- Administer the morning dose of SD-809 with a meal or light snack
- Collect a 12-lead ECG 3 hours after SD-809 administration following at least 5 minutes of rest in a supine or semi-recumbent position.
    - Based on the ECG machine reading, if QTcF value is >500 msec or there is a change from Baseline in QTcF value of >60 msec, two additional 12-lead ECGs should be collected as soon as practical. There should be at least 5 minutes between ECGs.
- Transmit ECGs to the central laboratory on the same day that they are collected.

6.7.2. Unscheduled Telephone Visit(s)

For unscheduled telephone visit(s) needed during Part A and Part B, the following activities should be performed:

- Assessment of adverse events, dyskinesia control, and concomitant medications in consultation with the subject and caregiver, if appropriate.

- Evaluation of study drug dose level and adjustment, if necessary (at the Investigator's discretion)
- Re-order study drug (at the Investigator's discretion) (see Operations Manual for further details)

For unscheduled telephone visit(s) needed during Part C, the following activities should be performed:

- Assessment of adverse events and concomitant medications in consultation with the subject and caregiver, if appropriate.

6.8. Efficacy and Quality of Life Measures

6.8.1. Abnormal Involuntary Movement Scale

The AIMS is an assessment tool used to detect and follow the severity of TD over time. The AIMS was originally developed by a consortium of clinical psychopharmacology researchers funded by the National Institute of Mental Health's (NIMH) Psychopharmacology Research Branch (Guy, 1976). While the original AIMS is widely used and accepted in clinical practice, the scale does not include detailed descriptors, and thus, can be difficult to implement in a clinical trial setting. Over the years, a number of authors have developed modifications and scoring conventions to help clinicians assess abnormal movements with the AIMS in a more uniform manner (Lane, 1985; Munetz and Benjamin, 1988).

For the present study, Auspex has proposed the use of AIMS descriptors (Appendix 2), which are consistent with those utilized in large trials in schizophrenia, and were developed based on the work of Munetz and Benjamin (Munetz and Benjamin, 1988). These descriptors have face validity in describing the severity of abnormal movements in TD and have been reviewed with key scientific experts in movement disorders and psychiatry, who uniformly agreed that they are appropriate for providing guidance to Investigators in grading the severity of TD in this study.

The AIMS is composed of 12 clinician-administered and -scored items (Appendix 2). Items 1 to 10 are rated on a 5-point anchored scale and consist of the following:

- Items 1-4 assess orofacial movements
- Items 5-7 deal with extremity and truncal dyskinesia
- Items 8-10 deal with global severity as judged by the examiner, and the patient's awareness of the movements and the distress associated with them

Items 11 through 12 are yes/no questions concerning problems associated with teeth and/or dentures, as such problems can be mistaken for dyskinesia.

A total score from items 1 to 7 (orofacial, extremity, and truncal movements) can be calculated and represent observed movements, with higher scores indicative of more severe dyskinesia. Item 8 can be used as an overall severity index; items 9 and 10 provide additional information with regard to patient incapacitation and awareness; and items 11 and 12 provide information that may be useful in determining lip, jaw, and tongue movements (Guy, 2000).

6.8.2. Independent Rating of Dyskinesia

To enable a systematic evaluation of the primary endpoint, the AIMS will be digitally video-recorded using a standard protocol at Baseline and at Weeks 6, 15, 28, 41, 54, and 158 (see Appendix 2).

The videos from Baseline and Weeks 6, 15, 28, 41, 54, 106, and 158 will be independently reviewed by a blinded central rater(s) who is an expert in movement disorders.
This process will allow for a systematic assessment of dyskinesia that is not influenced by subject reports of tolerability or efficacy. Videos will be recorded and submitted to the central rater in a blinded manner with respect to visit number, site, and date of recording. A detailed video protocol will be included in the study operations manual. A detailed video review charter will be established to ensure appropriate blinding and review procedures by the central video raters.

6.8.3. Clinical Global Impression of Change

The CGIC (Appendix 3) is a single-item questionnaire that asks the investigator to assess a subject's TD symptoms at specific visits after initiating therapy. The CGIC uses a 7-point Likert Scale, ranging from very much worse (–3) to very much improved (+3), to assess overall response to therapy.

6.8.4. Patient Global Impression of Change

The PGIC (Appendix 4) is single-item questionnaire that asks the patient to assess their TD symptoms at specific visits after initiating therapy. The PGIC uses a 7-point Likert Scale, ranging from very much worse (–3) to very much improved (+3), to assess overall response to therapy. In general, patient-rated global measures of change have face validity and have been shown to correlate with disability for a number of chronic conditions (Kamper, Maher, & Mackay, 2009).

6.8.5. Modified Craniocervical Dystonia Questionnaire

The CDQ-24 is a disease-specific quality of life questionnaire developed for use in patients with craniocervical dystonia, including both cervical dystonia (CD) and blepharospasm (BPS) (Muller et al, 2004). The CDQ-24 was selected for use in the present study because it includes domains which are relevant not only to CD and BPS, but to TD. The following domains are evaluated in the CDQ-24: stigma, emotional well-being, pain, activities of daily living, and social/family life. For the present study, the CDQ-24 has been modified (Appendix 5) such that the questions focus directly on the impact of TD (as opposed to CD/BPS) on quality of life.

6.9. Safety Evaluations

6.9.1. Demographics and Medical History

The subject's gender, year of birth, age, race, ethnic origin, and medical and surgical history will be transferred from data collected in the parent study. The subject's medical and surgical history will be updated at Baseline.

6.9.2. Physical Examination

A complete physical examination will be performed as specified in the Schedule of Events. A complete examination includes evaluation of the following systems/regions:

- General Appearance
- Skin
- Head, Eyes, Ears, Nose, Throat
- Neck: Lymph Nodes, pulses
- Respiratory
- Musculoskeletal
- Abdominal
- Extremities

- Cardiovascular

A **brief physical** examination includes evaluation of the cardiovascular, respiratory, and abdominal systems.

6.9.3. Complete Neurological Examination

A complete neurological examination will be performed as specified in the Schedule of Events. The neurological examination includes evaluation of the following:

- Mental status
- Cranial nerves
- Motor system (strength, tone posture)
- Coordination
- Gait and balance
- Tendon reflexes
- Sensation

6.9.4. Vital Signs

Vital signs to be assessed should include resting blood pressure, heart rate, respiratory rate, and temperature. Heart rate and blood pressure measurements should be taken only after a subject has rested quietly in a sitting position for at least 5 minutes.

6.9.5. Orthostatic Blood Pressure and Pulse

Orthostatic blood pressure and pulse will be recorded at Weeks 6, 54, 106, 158/ET, the Pre-withdrawal Visit, and EOT.

Orthostatic blood pressure and pulse will be assessed in the supine and standing positions. The subject should be supine for at least 5 minutes before the supine blood pressure and pulse are measured. Subjects will then move to the sitting position briefly to ensure that no symptoms occur, after which they will stand for 3 minutes. Standing blood pressure and pulse will be obtained after the subject has been in the standing position for at least 3 minutes.

6.9.6. Laboratory Tests

Blood and urine samples will be collected and tested for the items in Table 5 and applicable parameters will be calculated according to the Standard Operating Procedures (SOPs) at the central laboratory. If abnormal, screening labs may be repeated once to confirm the subject's eligibility. As specified in Table 5, certain lab results obtained in the parent study do not need to be repeated at screening for Study SD-809-C-20.

Table 5: Laboratory Tests

• Sodium	• Creatinine	• Albumin
• Potassium	• Total calcium	• Total bilirubin
• Chloride	• Phosphate	• Direct bilirubin
• Bicarbonate	• Uric Acid	• Alkaline phosphatase (ALP)
• Magnesium	• Cholesterol	• Alanine aminotransferase (ALT)
• Glucose	• Triglycerides	• Aspartate transaminase (AST)
• Blood urea nitrogen (BUN)	• Total Protein	• Lactate dehydrogenase (LDH)
Hematology		***Urinalysis***
• Hemoglobin		• Leucocytes
• Hematocrit		• Nitrites
• Red blood cell count (RBC)		• Urobilinogen
• Mean cell volume (MCV)		• Protein
• Platelets		• pH
• White cell count		• Blood
• Neutrophils		• Specific gravity
• Lymphocytes		• Ketone
• Monocytes		• Bilirubin
• Eosinophils		• Glucose
• Basophils		• Microscopic exam (if indicated)
Labs for screening purposes		***Lab results from parent study***
• Urine pregnancy tests (women of childbearing potential only)		• CYP2D6 genotype (blinded) • Prothrombin Time (PT) with International Normalized Ratio (INR) • Follicle Stimulating Hormone for post-menopausal women only. • Hepatitis B surface antigen (HBsAg)

6.9.7. 12-lead Electrocardiogram

All ECGs will be performed after at least 5 minutes rest in a supine or semi-recumbent position. 12-lead ECGs to assess safety will be collected according to the Schedule of Events. Heart rate and ECG intervals (PR, QRS, QT, and QTcF) and clinical interpretation will be assessed by the central reader.

6.9.8. Detecting Adverse Events

The occurrence of adverse events should be sought by non-leading questioning of the subject and caregiver during the study and may also be identified when the subject and/or caregiver spontaneously volunteered them. Open-ended, non-leading questioning of the subject is the preferred method to detect adverse events.

Suitable non-leading questions include:

- "How are you feeling?"
- "How have you been doing since your last evaluation?"
- "Have you taken any new medicines since your last evaluation? If so, why?"

Adverse events may also be detected by the medical staff through physical examination, evaluation of laboratory tests results, or other assessments. All adverse events occurring from signing of the Informed Consent Form (ICF) to the end of the study, regardless of suspected causal relationship to study drug, will be recorded in the source documentation and on the appropriate electronic Case Report Form (eCRF) page for subjects who are enrolled.

6.9.9. Rating Scales

Subject-completed assessments will be available in English, Spanish, Hungarian, German, Polish, Czech, and Slovakian.

6.9.9.1. Unified Parkinson Disease Rating Scale Part III – Motor Examination

The UPDRS (Appendix 6) is a comprehensive instrument used to assess the signs and symptoms of Parkinson's disease. The UPDRS is comprised of various patient- and clinician-based assessments of motor, cognitive, and behavioral symptoms. UPDRS questions pertaining to motor function will be used to screen and monitor study subjects for Parkinsonism.

6.9.9.2. Barnes Akathisia Rating Scale

The BARS (Appendix 7) is a widely used rating scale for evaluation of drug-induced akathisia. This scale includes an objective assessment, subjective measures, including self-awareness and distress, and a global clinical assessment (Barnes, 1989).

6.9.9.3. Hospital Anxiety and Depression Scale

The HADS (Appendix 8) is a self-administered instrument reliable for detecting states of depression and anxiety in an outpatient medical setting (Zigmond & Snaith, 1983). The HADS is recommended by the National Institute of Neurological Disorders & Stroke (NINDS) Common Data Elements for HD because it serves as a good screening measure, it has been widely used and it is relatively simple to complete. It focuses on subjective disturbances of mood rather than physical signs, and aims at distinguishing depression from anxiety. The scale consists of 14 items (7 each for anxiety and depression). Each item is rated on a 4-point scale ranging from 0 (not at all) to 3 (very often). Responses are based on the relative frequency of symptoms over the preceding week.

6.9.9.4. Columbia Suicide Severity Rating Scale

The C-SSRS (Appendix 9 and Appendix 10) is a Food and Drug Administration (FDA)–endorsed questionnaire to screen for suicidality in trials of central nervous system (CNS)–active compounds (The Columbia Suicide Severity Rating Scale; *Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials, DRAFT GUIDANCE*, September 2010). The C-SSRS is an interview by trained study personnel that should be done at Baseline and during the study as outlined in the Schedule of Events. The form provided at Screening collects the history of suicide (C-SSRS form version termed "baseline" (Appendix 9) and at subsequent visits uses a C-SSRS termed "Since the Last Visit" (Appendix 10).

6.9.9.5. Epworth Sleepiness Scale

The ESS (Appendix 12) is a self-administered questionnaire composed of eight questions that provides a measure of a subject's general level of daytime sleepiness (Johns, 1991). The ESS asks respondents to rate, on a 4-point Likert scale (0 – 3), their usual chances of dozing off or falling asleep in different situations or activities that most people engage in as part of their daily

lives. The total ESS score is the sum of 8 item-scores and can range between 0 and 24 with a higher score indicating a higher level of daytime sleepiness. Most people can complete the ESS, without assistance, in 2 or 3 minutes.

6.9.9.6. Montreal Cognitive Assessment (MoCA©)

The MoCA© (Appendix 11) is a validated rapid screening instrument for assessing mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA© is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

6.10. Pharmacokinetic Evaluations

Subjects experiencing a serious adverse event should have a single blood sample collected as soon as possible after the serious adverse event and within 48 hours of the last dose of study drug for the pharmacokinetic assessment of α- and β- HTBZ, if possible. The date and time of the last dose of study drug should be recorded along with the date and time of the sample collection. Subjects who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected for future pharmacokinetic assessment of α- and β- HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor. The date and time of the last dose of study drug should be recorded along with the date and time of the sample collection.

6.11. Subject Restrictions

6.11.1. Concomitant Medications

Prohibited Concomitant Medications

The following products should not be used within 30 days of Baseline (unless noted below) and throughout the study:

- Tetrabenazine (within 7 days of Baseline)
- Valbenazine
- AMPT
- Metoclopromide, promethazine, and prochlorperazine
- Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc.)
- MAOIs
- Levodopa or dopamine agonists
- Reserpine
- Medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
- Botulinum toxin (within 3 months of Screening)
- Any investigational drug

The drugs listed above and other drugs which are known to cause QT prolongation (see Appendix 14) should not be taken concomitantly with study drug. A washout period of 5 half-lives before the Baseline visit is required. A duration less than 5 half-lives must be approved by the Medical Monitor.

Allowed Concomitant Medications

Stable Dosing

Subjects receiving psychoactive medications (including, but not limited to, neuroleptics [see Appendix 16], benzodiazepines, anticonvulsants, and mood stabilizers) must be on a stable dose for ≥30 days (oral medication) before Screening and in the opinion of the treating psychiatrist, no changes in drug or dose are expected in the next 3 months. After 3 months, changes in psychoactive medications are allowed if approved by the Investigator. Any changes in concomitant medications must be documented in the eCRF.

Antipsychotics

Considering the potential of antipsychotic drugs to prolong the QT interval, additional ECG monitoring is required if the Investigator 1) increases the dose of a patient's current antipsychotic treatment, 2) switches the patient to a different antipsychotic treatment, or 3) adds a new antipsychotic treatment to the patient's regimen. In such cases, subjects should have an unscheduled visit within 1-2 weeks for a change in **oral** antipsychotic treatment, or have an unscheduled visit within 4-5 weeks, 8-9 weeks, or 12-13 weeks (depending upon the prescribed LAI) for a change in their **LAI** antipsychotic treatment, to have a repeat 12-lead ECG following their usual SD-809 dose (see Section 6.7.1).

Antidepressants

Subjects receiving antidepressant therapy must be on a stable dose for 45 days before Screening. Subjects receiving long acting (depot) medications must have been on stable therapy (dose, frequency) for ≥3 months before Screening.

Other

Female subjects on hormonal contraception (approved oral, transdermal, or depot regimen) for birth control must be on a stable dose for at least 3 months prior to Screening and through study completion.

Subjects will be instructed to inform the study Investigator of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF.

6.11.2. Use of Alcohol or Sedating Drugs

As with other VMAT2 inhibitors (tetrabenazine, reserpine), subjects should be advised that the concomitant use of alcohol or other sedating drugs with SD-809 may have additive effects and cause or worsen somnolence. Until subjects are receiving a stable dose of SD-809 and understand how the drug affects them, alcohol should be used with caution.

6.11.3. Other Restrictions

Subjects should be advised to not drive a car or operate dangerous machinery until they understand how SD-809 affects them.

Use of illicit drugs is prohibited from the time of signing of the Informed Consent Form or Assent and throughout study participation.

6.12. Caregiver Responsibilities

The Investigator will assess whether the subject lives in a stable environment and has adequate supervision when necessary to safely participate in the trial. For those subjects needing the assistance of a caregiver, the caregiver must interact on a regular basis with the subject and oversee study drug administration. In addition, the caregiver will assure attendance at study visits and participate in evaluations, as required.

The caregiver must also make him/herself available for clinic visits and telephone contacts in order to report dyskinesia control and adverse events to determine whether dose adjustment of study drug will be made. As subjects may have agnosia to dyskinesia, telephone contacts should involve the subject and caregiver, when appropriate.

6.13. Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time for any reason. A subject may be withdrawn from the study for any of the following reasons:

- Subject voluntarily discontinues study participation (subject withdrawal);
- The need to take medication which may interfere with study measurements;
- Intolerable/unacceptable adverse events (see Section 5.2.4 for QTcF discontinuation criteria);
- Major violation or deviation of study protocol procedures;
- Non-compliance of subject with protocol;
- Subject is unable to comply with study procedures;
- Withdrawal from the study is, in the Investigator's judgment, in the subject's best interest;
- Subject is lost to follow-up;
- A female subject becomes pregnant;
- Study termination by the Sponsor.

All subjects to be withdrawn from the study for medical reasons should be reviewed with the Medical Monitor. The reasons for withdrawal will be recorded on the eCRF and included in the final report along with any adverse events and any necessary medical treatment.

6.14. Discontinued Subjects

Notification of early subject discontinuation from the study and the reason for discontinuation will be made to the Clinical Monitor and will be clearly documented on the appropriate eCRF page. If a subject is discontinued from the study early, all ET evaluations should be performed at the time of discontinuation, if possible.

6.15. Study Termination

The study may be stopped at any time by the Sponsor, IEC/IRB, and/or regulatory agencies for any reason. The Sponsor reserves the right to discontinue the trial at any time for any reason. Reasons will be provided in the event of this happening. The Investigator reserves the right to discontinue the study at their site for safety reasons at any time in collaboration with the Sponsor.

7. ADVERSE EVENTS

Throughout the course of the study, all adverse events will be monitored and reported on an adverse event CRF, including assessments of seriousness, severity, action taken, and relationship to study drug. If adverse events occur, the first concern will be the safety of the study participants.
Adverse events will be recorded from the time of consent through the final study visit.
Information about side effects already known about the study drug can be found in the IB and will be included in the subject ICF.
The Investigator and site staff are responsible for detection, recording and reporting of events that meet the criteria and definition of an adverse event or serious adverse event (listed below).

7.1. Definitions

7.1.1. Adverse Event

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) therefore, can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.
Examples of an adverse event include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Abnormal safety assessments if they lead to study drug dose modification, study drug discontinuation or to therapeutic intervention (e.g., low hemoglobin that requires transfusions).
- Abnormal laboratory tests if they are associated with clinical signs, symptoms or if they lead to a diagnosis or therapeutic intervention.
- Abnormal vital signs if they are clinically significant and lead to a diagnosis or therapeutic intervention.
- Abnormal ECGs if they are clinically significant and lead to therapeutic intervention or diagnosis. The clinical significance should be confirmed by a cardiologist.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug product or a concurrent medication.

Examples of an adverse event do <u>not</u> include:

- A medical or surgical procedure (e.g., endoscopy); a condition that leads to the procedure is an adverse event.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to hospital) or scheduled elective procedures like cosmetic surgery are not adverse events. However, if the procedure results in an unexpected complication, the complication is an adverse event.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence did not occur or when signs are not expressing a medical problem but rather are expressing natural physiological responses (e.g., dyspnea after running, limb paresthesias due to awkward position).
- Signs, symptoms, or laboratory results that reflect an improvement of a past medical condition (e.g., sleeping better).

7.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3. Adverse Reaction

An adverse reaction means an adverse event that is caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.1.4. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the IB or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. “Unexpected”, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.5. Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death (i.e., the adverse event caused the death).
- Is life-threatening. The term life threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient overnight hospitalization or prolongation of an existing hospitalization, unless hospitalization is for:
    - Elective or pre-planned treatment for a pre-existing condition and has not worsened since signing the informed consent

  - Social reasons and/or respite care in the absence of any deterioration of the subject's general condition.
  - In general, hospitalization signifies that the subject has been detained (involving at least an overnight stay of at least 24 hours) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious.
- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect (i.e., an adverse finding in a child or fetus or a subject exposed to the study drug prior to conception or during pregnancy).
- Is medically important, defined as an event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above, or result in urgent investigation. Examples of such events are malignancies, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If either the Sponsor or Investigator believes the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

7.2. Recording of Adverse Events

Whenever possible, a unifying diagnosis should be recorded in the eCRF as the adverse event rather than individual signs or symptoms. Similarly, the unifying diagnosis should be recorded as the adverse event rather than the abnormal laboratory result (i.e., "anemia" instead of "low hemoglobin").

If the adverse event is a worsening of a past medical condition, the adverse event should clearly indicate that the past medical condition has worsened using words such as "worsening," "aggravated," or "exacerbation."

7.2.1. Recording of Non-Serious Adverse Events

Collection of adverse events will begin immediately following signing of the ICF through the final study visit. The Investigator will monitor each subject closely and record all observed or volunteered adverse events. Adverse findings detected at the Screening visit (e.g., abnormalities on clinical laboratory testing, ECGs, physical/neurological examination) will be recorded on the Medical History CRF and adverse events occurring after the Screening visit but before starting study treatment will be recorded on the adverse event CRF and considered non-treatment emergent.

7.2.2. Recording of Serious Adverse Events

Collection of serious adverse events will begin immediately following signing of the ICF through the final study visit. The Investigator will monitor each subject closely and record all observed or volunteered serious adverse events. Serious adverse events occurring after signing

the ICF but before starting study treatment will be considered non-treatment emergent.
If a new serious adverse event comes to the attention of the Investigator after the completion of the final study visit, information regarding the serious adverse event should be collected and reported to the Sponsor only if assessed as reasonably possibly related to the study drug(s) by the Investigator.
After the initial serious adverse event report, the Investigator is required to proactively follow each subject and provide further information to the Sponsor (or designee) on the subject's condition. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the serious adverse event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
Serious adverse events that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. All serious adverse events will be followed:

- Until resolution, or
- For 28 days after the subject's last follow-up visit, or
- If, in the investigator's opinion, the condition is unlikely to resolve, whichever comes first. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

Subjects experiencing a serious adverse event should have a single blood sample collected as soon as possible after the serious adverse event and within 48 hours for the pharmacokinetics of α- and β-HTBZ, if possible. The date and time of the last dose of study drug should be recorded along with the date and time of the sample collection.

7.3. Evaluation of Adverse Events (Serious and Non-Serious)

At each in-person visit and telephone contacts, occurrence of adverse events will be assessed by verbally asking subjects and caregivers if they have had any problems or symptoms since their last visit.
If the subject or caregiver reports an adverse event, the investigator/coordinator will probe further to determine:

- Time of onset and resolution
- Frequency
- Causality/relation to study treatment
- Intensity
- Action taken regarding study drug
- Outcome

7.3.1. Severity

The Investigator will make an assessment of intensity for each adverse event and serious adverse event reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each adverse event and serious adverse event recorded in the eCRF should be assigned to one of the following categories:

- **Mild: Causes minimal discomfort, but does not interfere with normal daily activities**
- **Moderate: Causes sufficient discomfort to interfere with normal daily activities**
- **Severe: Prevents normal daily activities**

An adverse event that is assessed as severe should not be confused with a serious adverse event.

Severity is a category utilized for rating the intensity of an event; and both adverse events and serious adverse events can be assessed as severe. An event is defined as serious when it meets one of the pre-defined outcomes as described in Section 7.1.5.

7.3.2. Relationship to Study Drug

The Investigator is obligated to assess the relationship between study drug and the occurrence of each adverse event. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the drug caused the adverse event. The investigator's assessment of the relationship of each adverse event to study drug will be recorded it in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The Medical Monitor's opinion may be sought in those cases in which the Site Investigator is unable to make an independent judgment. The Medical Monitor may in turn consult with the Principal Investigator as needed. The following definitions are general guidelines only to help assign grade of attribution:

- **Unrelated:** The adverse event is **clearly not related** to the investigational drug
- **Unlikely:** The adverse event is **doubtfully related** to the investigational drug
- **Possible:** The adverse event **may be related** to the investigational drug
- **Probable:** The adverse event **is likely related** to the investigational drug
- **Definite:** The adverse event **is clearly related** to the investigational drug

7.3.3. Action Taken with Study Treatment

Action taken as a result of an adverse event will be recorded on the adverse event eCRF as follows:

- No change
- Dose reduced
- Drug suspended (see Section 5.2.4 for guidance in contacting Medical Monitor)
- Drug permanently discontinued

7.3.4. Treatment Required

Treatment required as a result of an adverse event will be recorded in the subject's source documents, and if medication is required, on the concomitant medications log:

- None
- Medication Required (record on Concomitant Medications eCRF)
- Hospitalization Required
- Other (specify)

If a diagnosis has been entered as an adverse event, the treatment(s) recorded may represent the treatment(s) given for one or more sign(s) or symptoms(s) (e.g., Naproxen for the adverse event "fracture", without recording "pain due to fracture" or "inflammation due to fracture" as separate adverse events).

7.3.5. Outcome

Outcome of an adverse event will be recorded on the adverse event eCRF as follows:

- Recovered / Resolved
- Recovering / Resolving
- Recovered / Resolved with Sequelae

- Not Recovered / Not Resolving
- Fatal
- Unknown

7.4. Procedures for Reporting Serious Adverse Events

All serious adverse events occurring during study participation must be reported to the Sponsor (or designee) and to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities.

7.4.1. Completion and Transmission of the Serious Adverse Event Report

Once an Investigator becomes aware that a serious adverse event has occurred in a study subject, she/he will report the information to the Sponsor (or designee) within 24 hours. The serious adverse event form (provided in the study Operations Manual) will always be completed as thoroughly as possible with all available details of the event, signed by the Investigator (or designee), and forwarded to the Sponsor (or designee) within the designated time frames. If the Investigator does not have all information regarding a serious adverse event, he/she will not wait to receive additional information before notifying the Sponsor (or designee) of the event and completing the form. The form will be updated when additional information is received Whenever possible, the Investigator will provide an assessment of causality at the time of the initial report as described above.

The Sponsor will provide a list of project contacts for serious adverse event receipt. Any event that in the opinion of the Investigator may be of immediate or potential concern for the subject's health or well-being will be reported to the Sponsor (or designee).

7.4.2. Regulatory Reporting Requirements for Serious Adverse Events

The Investigator must promptly (within 24 hours of awareness) report all serious adverse events to the Sponsor (or designee) in accordance with the procedures describe above. Prompt notification of serious adverse events by the Investigator to the appropriate project contact for serious adverse event receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met. The Investigator will be responsible for reporting serious adverse events to the IRB/IEC per local regulatory requirements.

The Sponsor (or designee) is responsible for reporting serious adverse events to the relevant regulatory authorities in accordance with local regulations. That is, serious adverse events which are determined by the Sponsor to be "Unexpected" and classified as "Suspected Adverse Reactions" will be reported in an expedited manner.

7.5. Procedures for Reporting Pregnancy Exposure and Birth Events

The Investigator must promptly report all pregnancies in female study subjects to the Sponsor (or designee) in accordance with the Operations Manual. While the pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complications should be recorded as adverse events or serious adverse events. Any pregnancy will be followed through its conclusion for observation of any serious adverse events including congenital anomalies/birth defects.

8. STATISTICAL PROCEDURES AND DATA ANALYSIS

This section describes the statistical analysis strategy and procedures for the study. Summary statistics will be provided by prior treatment (in parent study) and for the overall population. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. Details of the data analysis will be described in a separate Statistical Analysis Plan.

8.1. Analysis Populations

Safety Population: The Safety Population will include all subjects who were administered any study drug. Subjects who are assigned a subject number but withdrew prior to dosing will not be included in the Safety Population. If relevant, details of their participation and reason for withdrawal will be listed separately in the study report.
All summaries of safety endpoints in will be summarized descriptively in the Safety Population.
Intent-to-Treat (ITT) Population: The ITT Population will include all enrolled subjects in the study. All efficacy measures in Part A will be summarized using the ITT Population.
Randomized Withdrawal ITT Population: The Randomized Withdrawal ITT Population will include all subjects enrolled to Part B of the study.
Randomized Withdrawal Modified Intent-to-Treat (mITT) Population: The Randomized Withdrawal mITT Population will include all subjects enrolled to Part B who receive study drug during the Randomized Withdrawal Period and have a centrally read AIMS score at both the Pre-withdrawal Visit and the Post-withdrawal Visit. All efficacy measures in the Randomized Withdrawal Period will be analyzed using the Randomized Withdrawal mITT Population.

8.2. Demographics and Baseline Data

Demographic information will be presented for each subject. Medical/surgical history data at baseline will be listed, as will physical examination data.

8.3. Safety Analyses

Safety and tolerability will be assessed throughout the study by monitoring the following parameters:

- Adverse events
- Clinical laboratory tests
- Physical examination
- Vital signs
- 12- lead ECGs
- UPDRS – Motor Examination
- BARS
- HADS
- C-SSRS
- ESS
- MoCA©

Safety data will be summarized descriptively for the overall population and based on prior treatment (SD-809 or placebo) in the parent study. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. Descriptive statistics of change-from-baseline will use the Baseline from the present study (SD-809-C-20 Baseline).
The nature, frequency, and severity of adverse events will be tabulated for all subjects combined and by treatment. Baseline, within study, end of study, and change-from-baseline values for

clinical laboratory evaluations and vital signs will be summarized as appropriate. Treatment-emergent adverse events and laboratory, vital sign, and ECG parameters will be summarized. In addition, change from baseline will be summarized for laboratory and vital sign parameters. Shift tables will be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized.

8.4. Safety Endpoints

The following safety endpoints will be assessed in Part A:

- Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, adverse events leading to withdrawal during the following periods:
  - Overall
  - During titration
  - During long-term treatment
- Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Observed values and changes from baseline in vital signs
- Observed values in ECG parameters and abnormal findings
- Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms
- Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA©
- Duration of time to achieve stable dosing of SD-809

The following secondary safety endpoints will be assessed in Part B:

- Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, and adverse events leading to withdrawal
- Observed values and changes from start of randomized withdrawal in clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Observed values and changes from start of randomized withdrawal in vital signs
- Observed values in ECG parameters and abnormal findings
- Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms
- Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA©

The following secondary safety endpoints will be assessed in Part C:

- Secondary safety endpoints:
  - Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, and adverse events leading to withdrawal from start of Part C
  - Observed values and changes in vital signs from start of Part C
  - Observed values and changes in C-SSRS from start of Part C
  - Observed values in ECG parameters and abnormal findings from start of Part C

- Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms from start of Part C

8.5. Efficacy Measures

The following efficacy measures will be assessed during Part A:

- The change in AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by the site rating.
- The proportion of subjects who are a treatment success based on the CGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study.
- The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline of this study at each visit that this is measured.
- The change in the modified CDQ-24 score from Baseline of this study at each visit that this is measured.
- The proportion of subjects who are a treatment success based on the PGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study.
- The percent change in AIMS score from Baseline of this study at each visit that this is measured.

The following efficacy measure will be assessed during Part B (Randomized Withdrawal Period):

- Primary efficacy endpoint: change from Pre-withdrawal Visit AIMS scores (items 1 through 7) as assessed by blinded central video rating to the Post-withdrawal Visit between subjects treated with SD-809 and subjects treated with placebo.

8.6. Efficacy Analysis (Randomized Withdrawal Period; Part B)

Analysis of the change in centrally read AIMS score (items 1 through 7) during the Randomized Withdrawal Period (from the Pre-withdrawal Visit to the Post-withdrawal Visit) will use an analysis of covariance (ANCOVA) model with the change in AIMS score as the dependent variable. The model will include randomized withdrawal treatment group, AIMS score at the Pre-withdrawal Visit, and DRA status at the Pre-withdrawal Visit as fixed effects. The least squares means of the change in AIMS score will be compared between the SD-809 treatment and placebo groups using a 2-sided test at the alpha=0.05 level of significance. In addition, actual values and changes in AIMS score will be summarized using descriptive statistics.

The primary efficacy analysis will be tested at the α=0.05 level. If less than 135 subjects are enrolled into the randomized withdrawal portion of the study, inferential statistics will not be provided as the study will be insufficiently powered to detect a treatment effect given the sample size assumptions.

8.7. Sample Size

Because this is an open-label safety study, the sample size is not based on statistical considerations.

During the Randomized Withdrawal Period in Part B, there will be up to 194 subjects randomized (SD-809 or placebo). It is estimated that approximately 91 subjects per arm will enable a power of at least 90% to detect a beneficial effect of 1.4 points or more in the change

from pre-withdrawal to post-withdrawal in centrally read AIMS when the SD-809 arm is compared to placebo, assuming a standard deviation of 2.9 and a 2-sided type I error rate of 5%. Approximately 102 subjects may enroll in Part C conducted in the EU countries.

8.8. Protocol Deviations and Violations

The Investigator is responsible for ensuring that the study is conducted in accordance with the protocol. No modifications to the protocol, other than those that are deemed necessary to protect the safety, rights, or welfare of subjects by the Investigator are to be made without prior, written approval by the Sponsor. The nature and reasons for the protocol deviation will be recorded where appropriate and indicated. The Sponsor must be notified of all protocol deviations/violations. Significant protocol deviations/violations (e.g., inclusion/exclusion criteria) will be reported to the Sponsor and to the IRB/IEC in accordance with its reporting policy.

8.9. Data Recording

Source data will be transcribed onto source document worksheets and will then be entered into an eCRF. An Electronic Data Capture (EDC) system with eCRFs will be used for this trial. Instructions for eCRF completion will be provided in a separate document. Source data collection and entry into the eCRF will be completed by authorized study site personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study site personnel prior to the study being initiated and before any data is entered into the eCRF system for any study subjects.

8.10. Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified clinical Investigators and appropriate study sties, review of protocol procedures with the clinical Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor (or designee) will review data accuracy and completeness during and after the study, and any discrepancies will be resolved with the clinical investigator or designee as appropriate.

8.11. Data Management

The data will be entered into a validated EDC system that complies with Title 21 of the Code of Federal Regulations part 11, maintained by the Sponsor or designee. The data management group will be responsible for data processing, in accordance with agreed procedures. The Principal Investigator will electronically sign and date the appropriate eCRF page when instructed to do so by the study CRA. This signature will indicate that the Principal Investigator inspected or reviewed the data in the database, the data queries, and the site notifications, and agrees with the content.

The standard procedures for handling and processing eCRF records will be followed per Good Clinical Practice (GCP) and the Sponsor’s (or designee’s) SOPs.
Complete details of data management will be described in a separate Data Management Plan.

9. ADMINISTRATIVE ISSUES

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines including the International Conference on Harmonization (ICH) Guideline on GCP. The clinical trial will be conducted in accordance with the applicable regulations of the local regulatory authority.

9.1. Investigator Obligations

9.1.1. Independent Ethics Committee/Institutional Review Board Approval

Prior to initiation of the study, the written IEC/IRB approval of the protocol and Study Information Forms/Informed Consent Forms based on the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) will be received. This approval will be on the Institutional letterhead and will refer to the Study Information Forms/Informed Consent Forms and to the study by title and protocol number given on page 1 of the protocol. A copy of the signed and dated letter of approval will be provided to Auspex and designee prior to study commencement. Any written information and/or advertisements to be used for volunteer recruitment will be approved by the IEC/IRB prior to use.

9.1.2. Written Informed Consent

Informed consent will be obtained before the subject can participate in the study. If subject lacks the capacity to provide informed consent, a LAR must provide written informed consent and the subject must provide assent. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

It is the responsibility of the Investigator or designee to obtain written informed consent, using the most current informed consent form approved by the IRB/IEC and Sponsor, from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator or designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting written consent will be provided by the Investigator or designee.

For this study, each eligible subject will be required to provide written informed consent utilizing: Consent to participation in the study (Information Form/Informed Consent Form).

All eligible subjects and caregivers will have the study explained by the Investigator or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomfort, risks, and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study. The subject and caregiver will be given a copy of the signed Information Form/Informed Consent Form to retain.

<u>Part B Double-Blind, Randomized Withdrawal Period</u>

Part B will begin after Amendment 06 implementation. Subjects who decline to participate in the Randomized Withdrawal Period (Part B) (i.e., sign written informed consent) will continue in Part A until Week 158.

Part C Reduced Burden Safety Assessments
Part C will begin after Amendment 07 implementation. Subjects who decline to participate in Part C (i.e., do not sign written informed consent) will complete the study at the Part B Follow-up Call.

9.1.3. Emergency Contact with Investigator
Suitable arrangements will be made for subjects to make contact with the Investigator or a medically qualified designee in the event of an emergency.

9.1.4. Ethical Considerations
This study will be carried out in accordance with the principles of ICH GCP which build upon the ethical codes contained in the Declaration of Helsinki.
The investigational site and the Sponsor agree to abide by the applicable guidelines for compensation for injury resulting from participating in a company-sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability.

9.1.5. Privacy Rule
All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.
Subject names will not be supplied to the Sponsor. Only the subject number and/or randomization number will be recorded on the source documents and eCRF. If the subject name appears on any other document (e.g., pathologist report), it must be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, IEC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws. Laboratory specimens, including CAG repeat testing, will be destroyed after testing is complete in accordance with each laboratory's standard procedures.

Digital video data is considered identifiable data (contains faces). Subjects will be informed in writing that video data will be analyzed by specific TD experts, and may be reviewed by the FDA. Sponsor medical personnel may access video data for review and analysis; however, videos will not be used by sponsor for any commercial, advertising or promotional purposes. Copies of the digital video data compiled and held for purposes of conducting this study will be handled in the strictest confidence and stored in accordance with local data protection laws.

If the results of the study are published, the identity of all subjects will remain confidential. The Investigator will maintain a list of the subject identification number to enable subjects' records to be identified.

9.2. Protocol Amendments
Any amendments to the protocol must be agreed upon by the Sponsor. Protocol amendments, if any, will be formalized and submitted to the IRB/IEC, per local rules, for written approval before implementation. The expedited review procedure for an amendment is appropriate only if subject safety is not an issue.

9.3. Records Retention

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or the Sponsor's standards/procedures; otherwise, the retention period will default to the time period specified in 21 CFR Part 312.57: 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

9.4. Study Monitoring

The Sponsor (or designee) is responsible for assuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the eCRFs. Subject confidentiality will be maintained.

In accordance with applicable regulations, GCP, and Sponsor (or designee) procedures, the clinical trial coordination center (CTCC) will contact the site prior to the subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate. The visits will be conducted in accordance with the Sponsor's (or designee's) SOP and study monitoring plan. In general, the Investigator agrees to fully cooperate with the monitor, allow the monitor direct access to all relevant documents, to allocate his/her time and the time of his/her staff to the monitor to discuss any findings and any relevant issues as needed.

9.5. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies. Examples of a clinical product complaint include but are not limited to the following:

- Suspected contamination
- Questionable stability (e.g., color change, flaking, crumbling, etc)
- Defective or incorrect packaging/labels
- Missing or extra units (e.g., primary container is received at the site with more or less than the designated number of units inside)
- Unexpected or unanticipated taste or odor or both

9.5.1. Product Complaint Reporting and Documentation

Each investigational site is responsible for reporting a suspected clinical product complaint to the Sponsor as soon as feasible and, if possible, within 48 hours of becoming aware of the issue. The following information should be provided to the Sponsor:

- Investigational site number, principal investigator name, and clinical protocol number

- Date of and name of person receiving the complaint
- Name, phone number, and address of the source of the complaint
- Product name and strength
- Description or nature of complaint
- Subject identifier and corresponding visit number, if applicable
- Subject number, bottle, and kit numbers (if applicable)
- Product available for return: Yes/No
- Product was taken or used according to protocol: Yes/No
- Associated serious adverse event: Yes/No

Note: Reporting a complaint must not be delayed if any of the above required information is not known within 48 hours of becoming aware of the complaint. The Sponsor will collaborate with the Investigator to obtain any outstanding information.

The Investigator will record in the source documentation a description of the clinical product complaint and any actions taken to resolve the complaint and to preserve the safety of the subject.

9.5.2. Handling the Suspect Study Drug at the Investigational Site

The Investigator must retain the product in question in a location separate from the Investigator's clinical study supplies. The Sponsor may request that the Investigator return the product for further evaluation and/or analysis.

The integrity of the randomization code and corresponding blinded clinical supplies must be maintained whenever possible.

9.5.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event, the protocol should be followed.

9.5.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor (or designee) may conduct a Quality Assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection is requested, the Investigator and institution agree to immediately notify the Sponsor, to allow the auditor/inspector direct access to all relevant documents, and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues and remedies.

10. INFORMATION DISCLOSURE AND INVENTIONS

10.1. Ownership

All information provided by Auspex, and all data and information generated by a study site and/or by Auspex's contractors and subcontractors as part of the study (other than a study subject's medical records), are the sole property of Auspex.

All rights, title and interests in any inventions, discoveries, know-how and other intellectual or industrial property rights which are conceived or reduced to practice during the course of or as a result of the study are the sole property of Auspex and are hereby assigned to Auspex.

If any written contract is executed between Auspex and the study site for the conduct of the study, or between Auspex and a contractor for support of the study, and such contract includes ownership provisions that are inconsistent with or otherwise differ from the foregoing sentence, then with respect to such inconsistency or difference, that contract's ownership provisions regarding inventions and other intellectual or industrial property rights shall control.

10.2. Confidentiality

All information provided by Auspex and all data and information generated by the site as part of the study, (other than a subject's medical records), will be kept confidential by the Investigator and other site staff. The Investigator or other site personnel will not use this information and data for any purpose other than conducting the study. These restrictions do not apply to:

(1) information which becomes publicly available through no fault of the Investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

10.3. Publication

Auspex recognizes the importance of communicating medical study data and therefore encourages publication in peer-reviewed scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts and presentations based on the data from this trial are described in the Clinical Trial Agreement.

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12. APPENDICES

Appendix 1: Site Investigator Signature Page

- I agree to implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- I have read and agree to comply with the Investigator obligations stated in this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of subjects.
- I agree to conduct in person or to supervise the trial.
- I agree to ensure that all that assist me in the conduct of the study are aware of their obligations.
- I agree to maintain all information supplied by Auspex Pharmaceuticals, Inc. in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read and understand Protocol SD-809-C-20 Amendment 07 in its entirety and I agree to all aspects.

Investigator:

_____
Print Name

_____ _____
Signature Date

Appendix 2: [redacted]

[redacted]

[h] Guy W. AIMS: ECDEU Assessment Manual for Psychopharmacology. Washington, DC: Government Printing Office; 1976.

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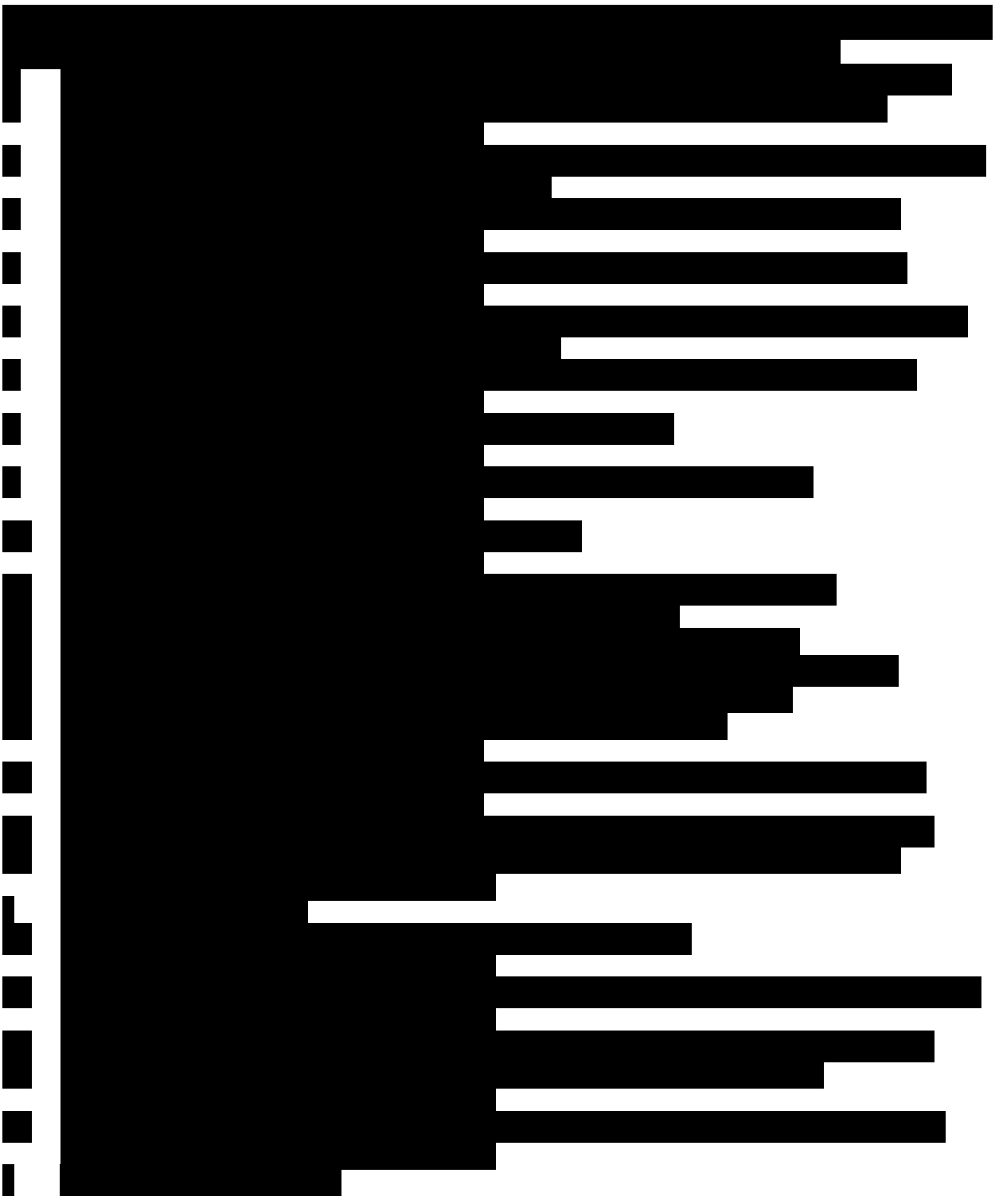

Appendix 6: Unified Parkinson's Disease Rating Scale (UPDRS) PART III: Motor Examination[i]

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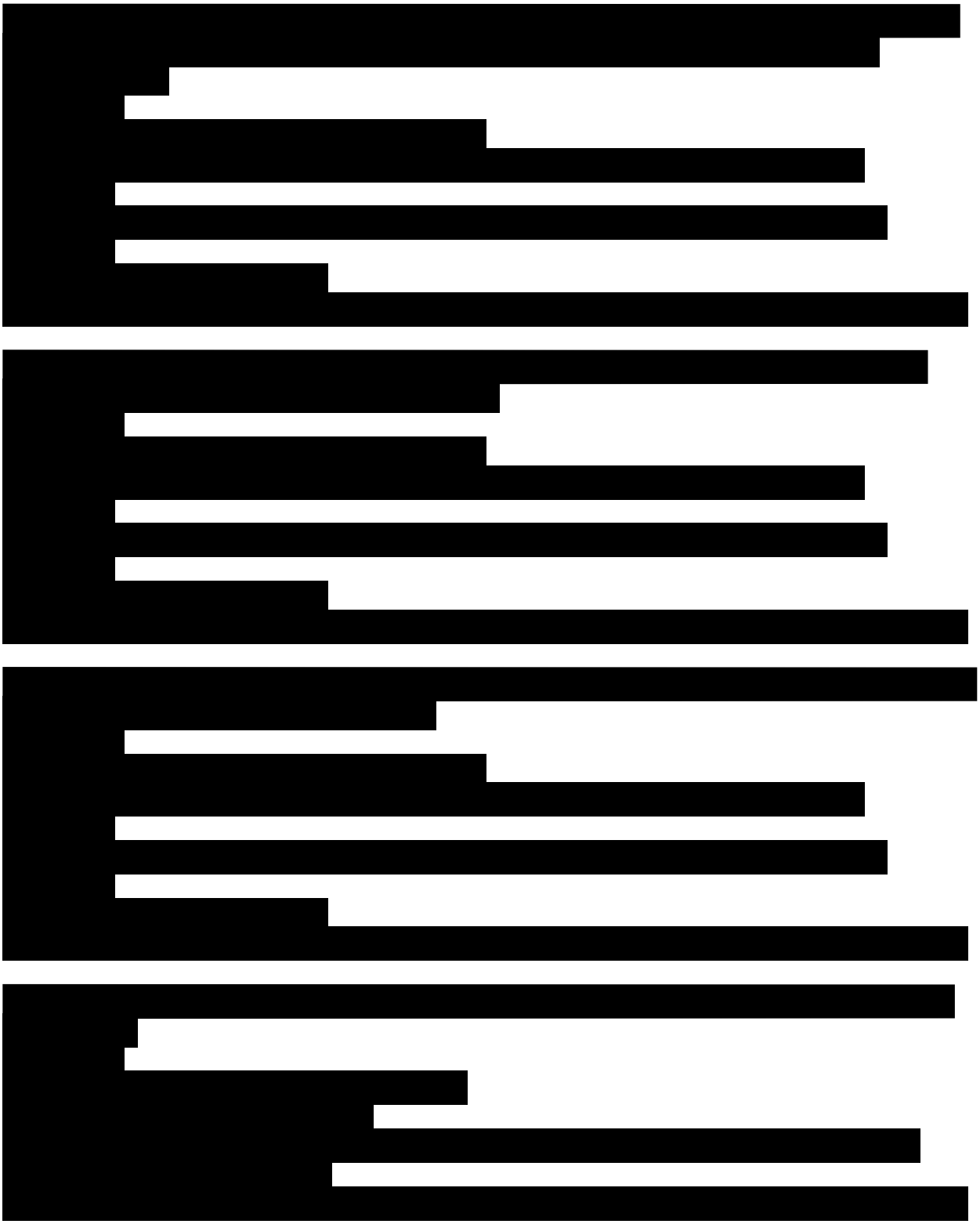
20c. Tremor at rest – Left hand



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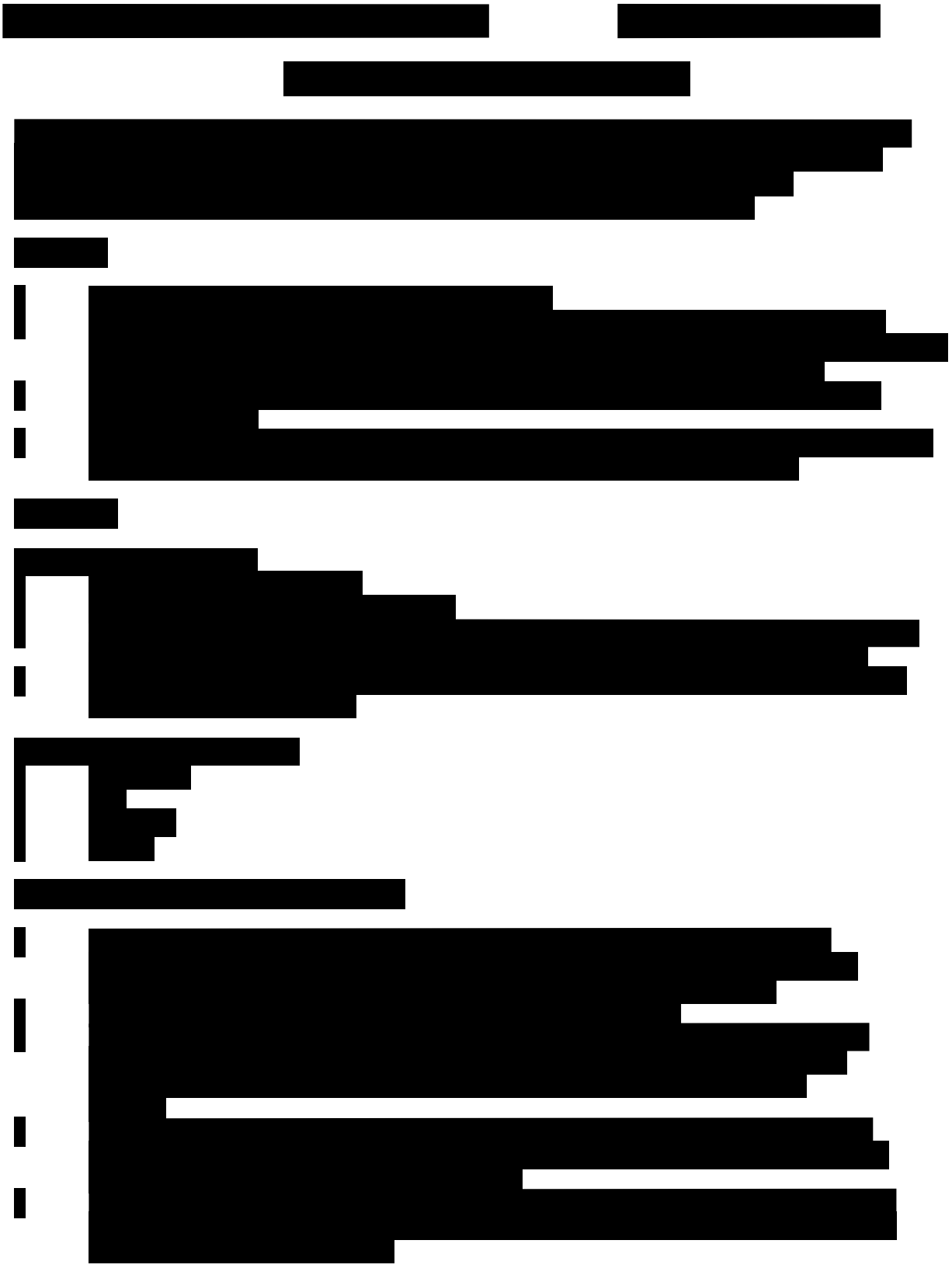

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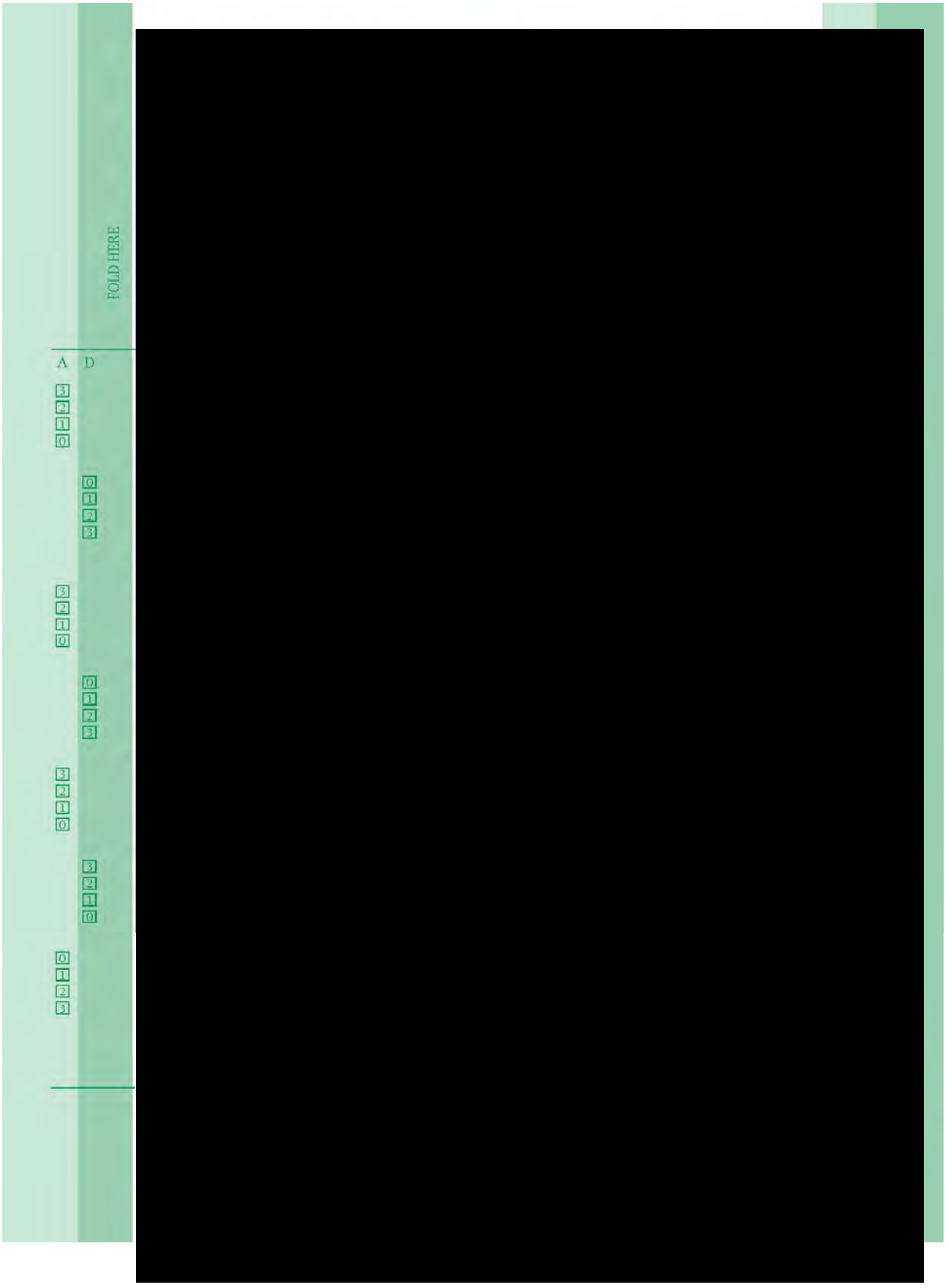

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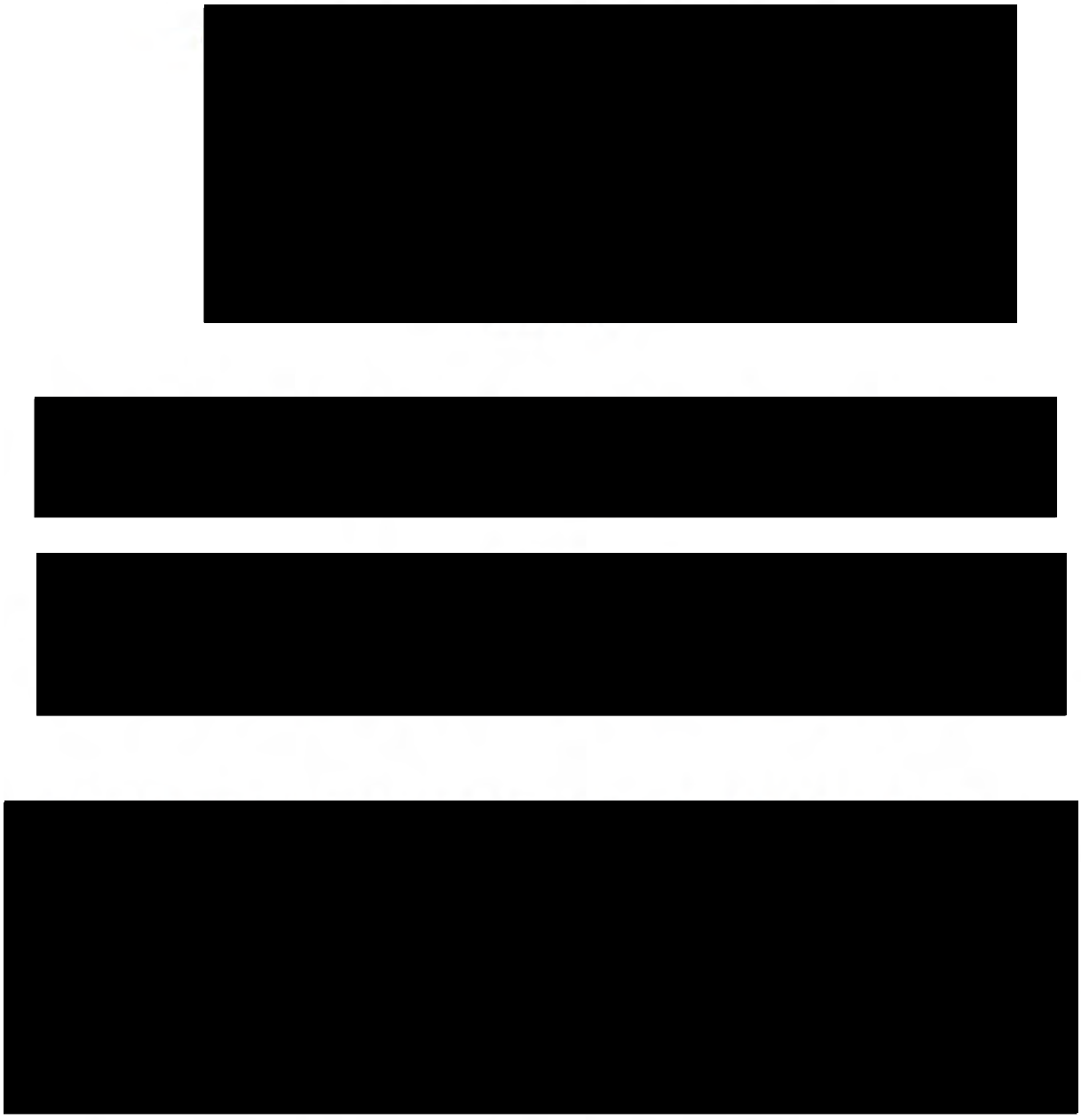

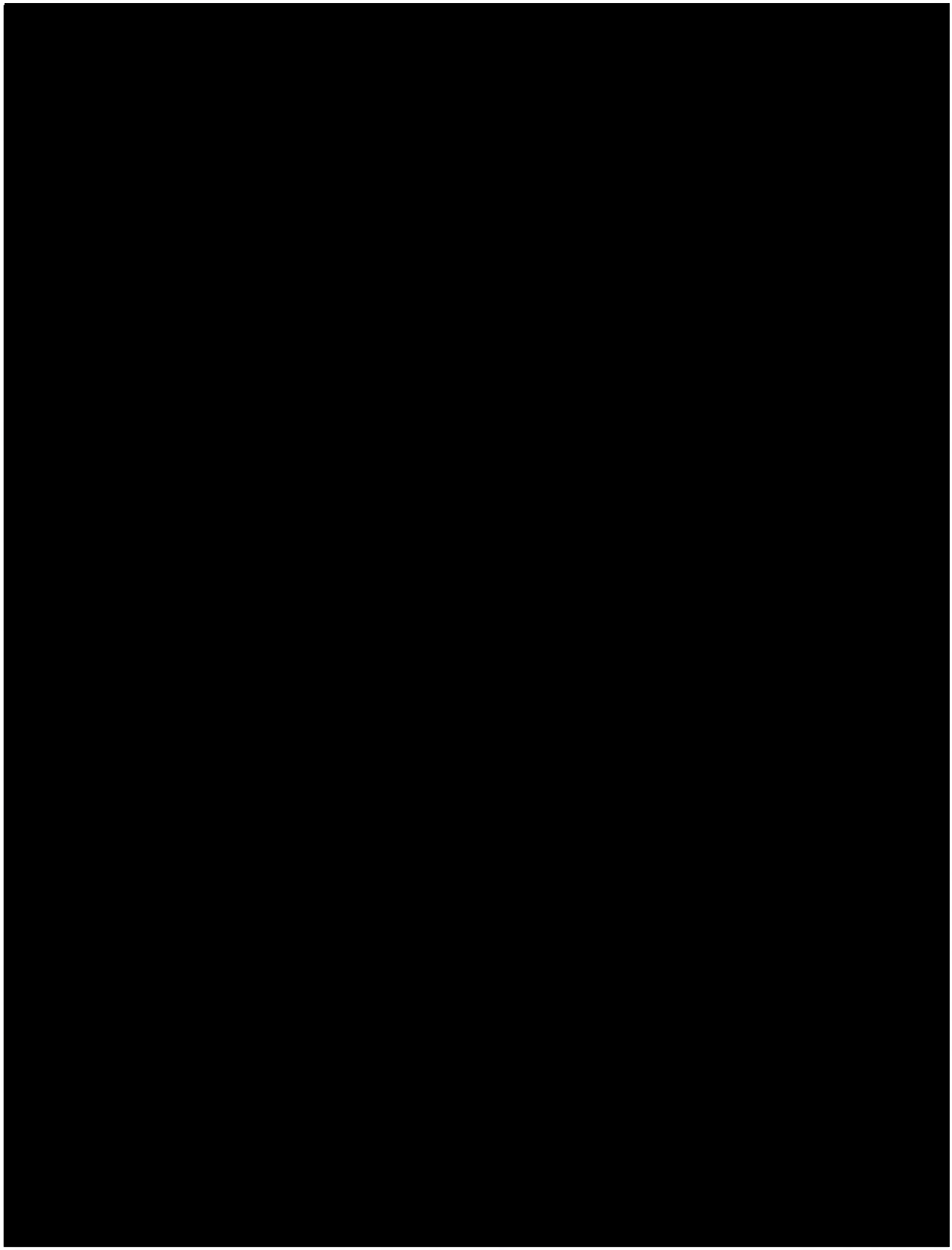

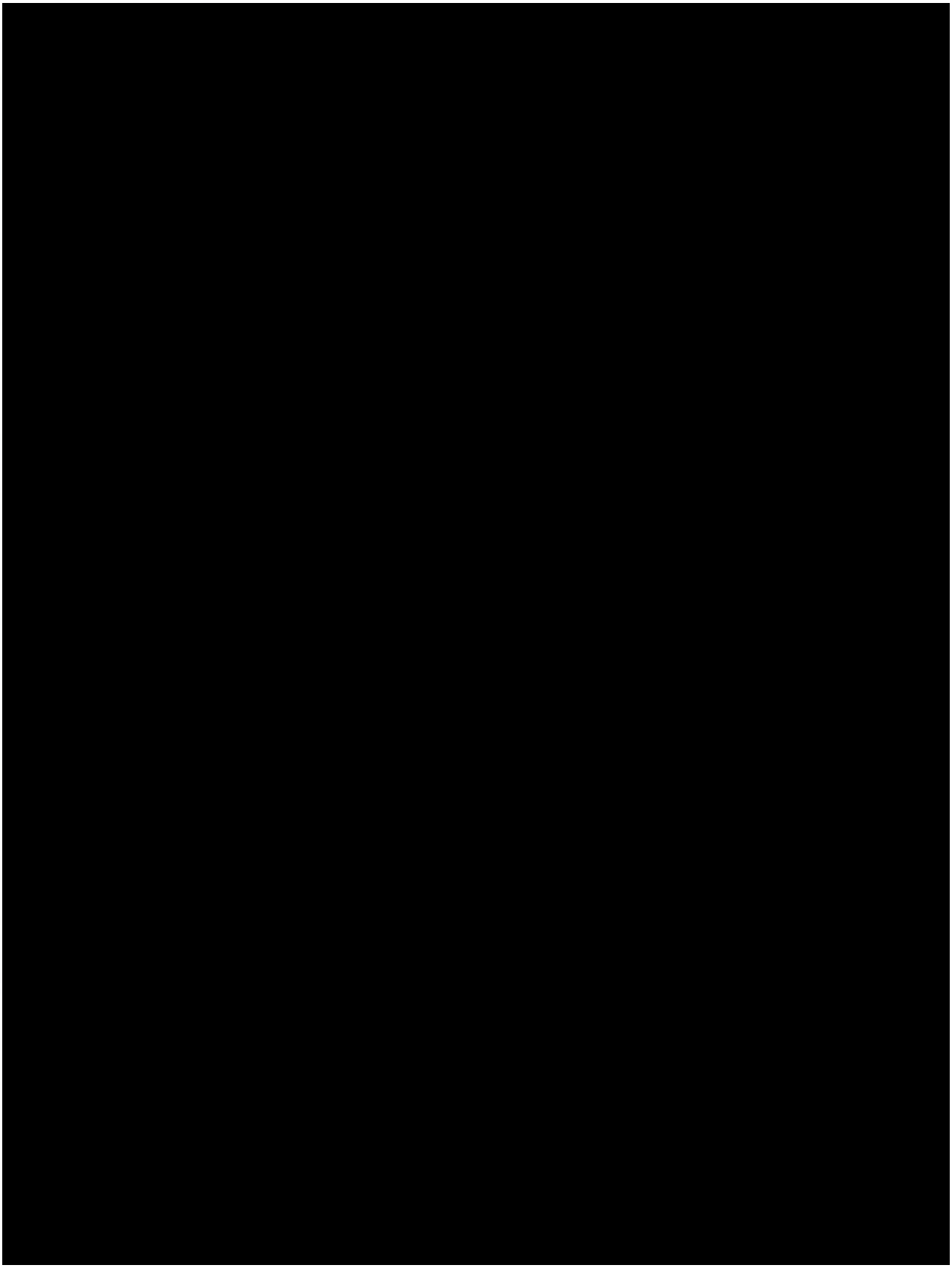

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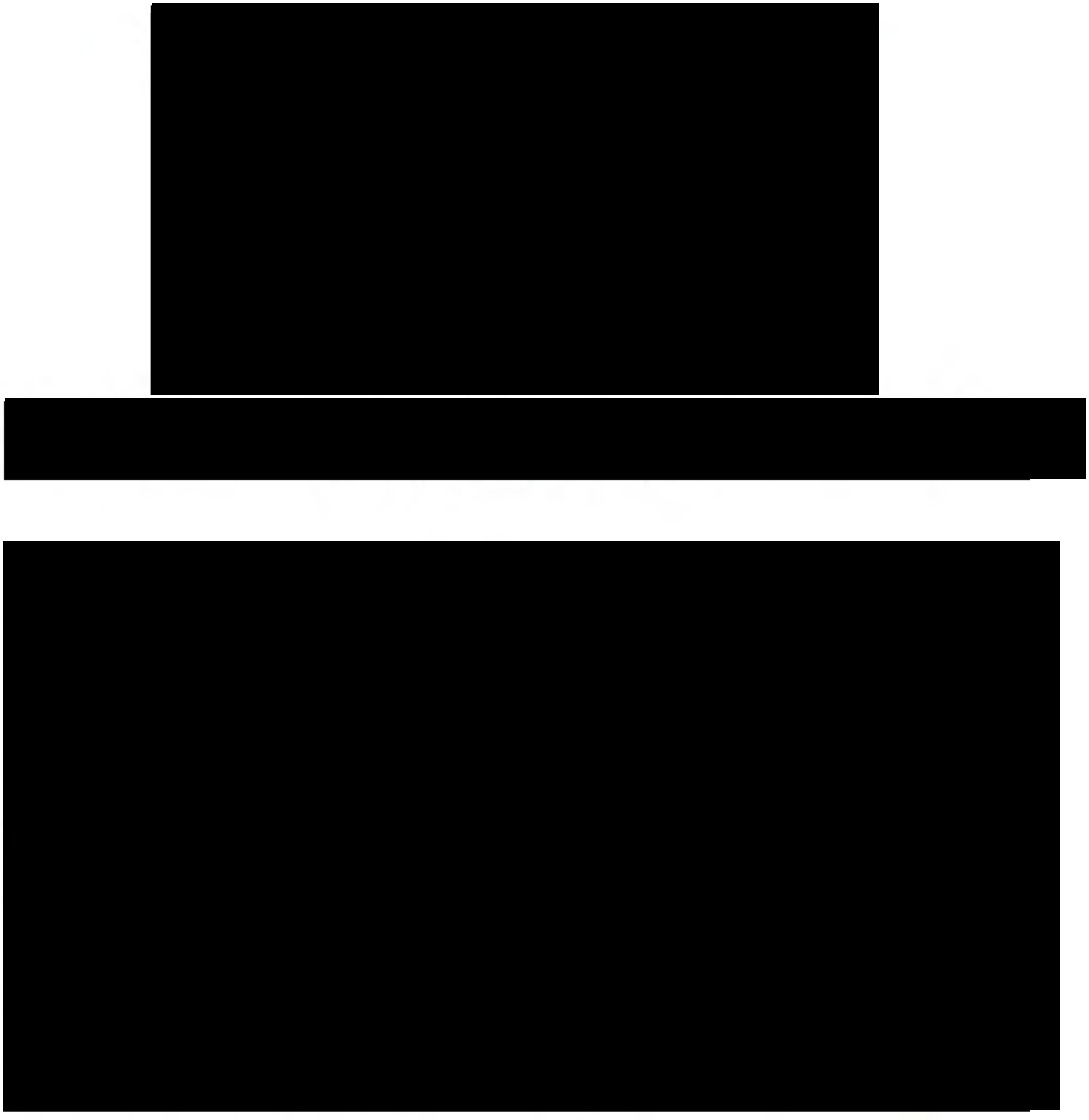

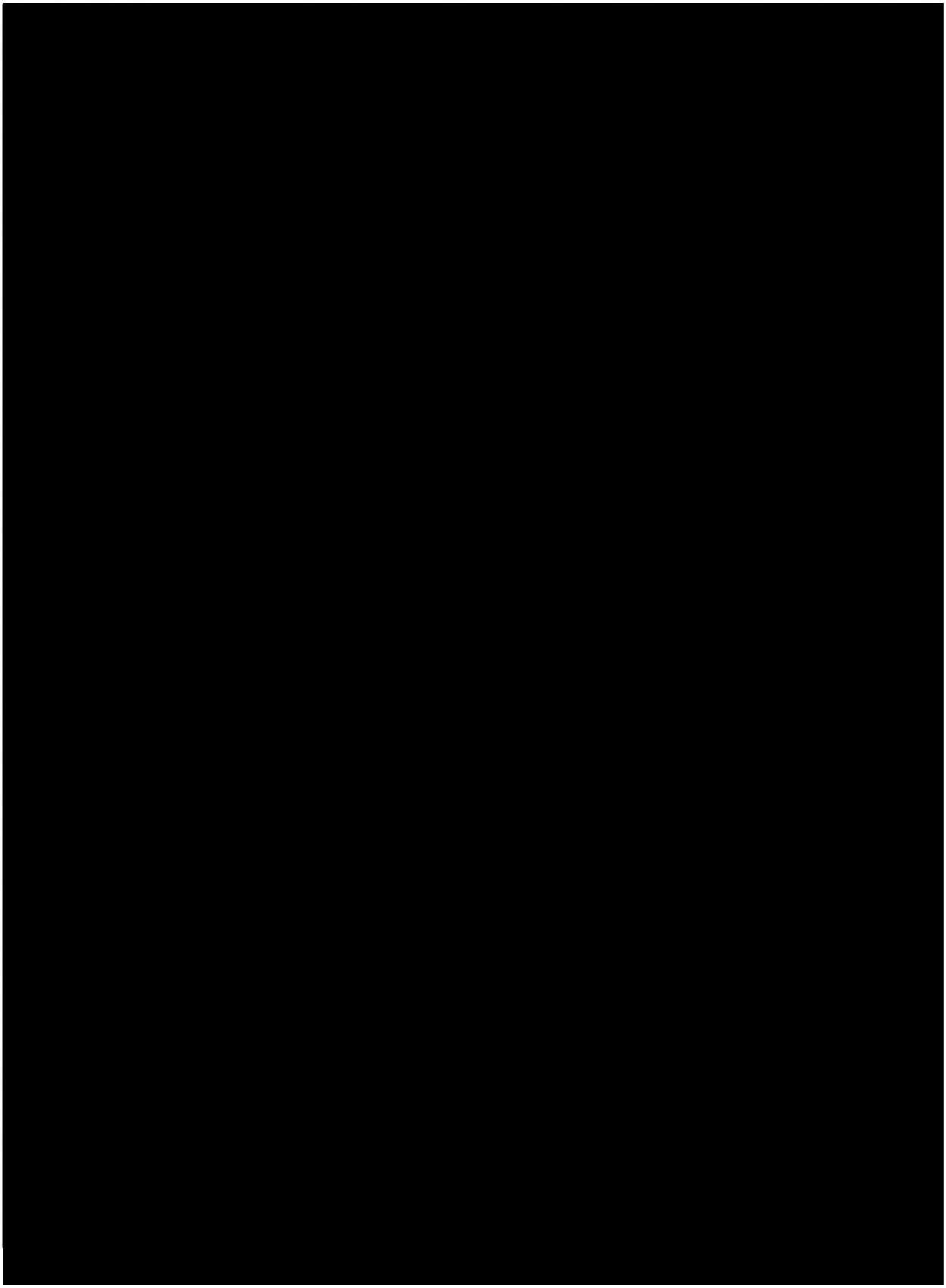

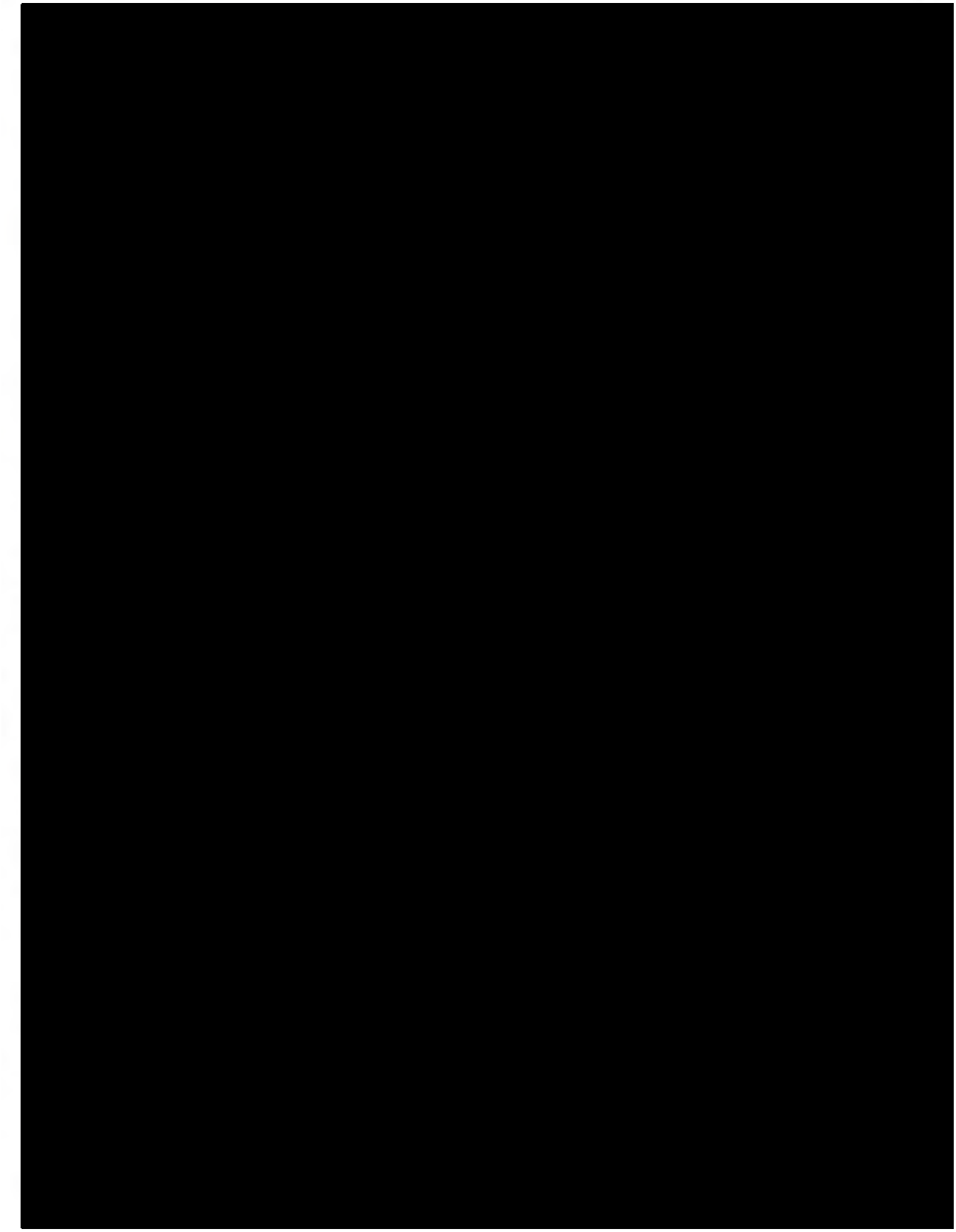

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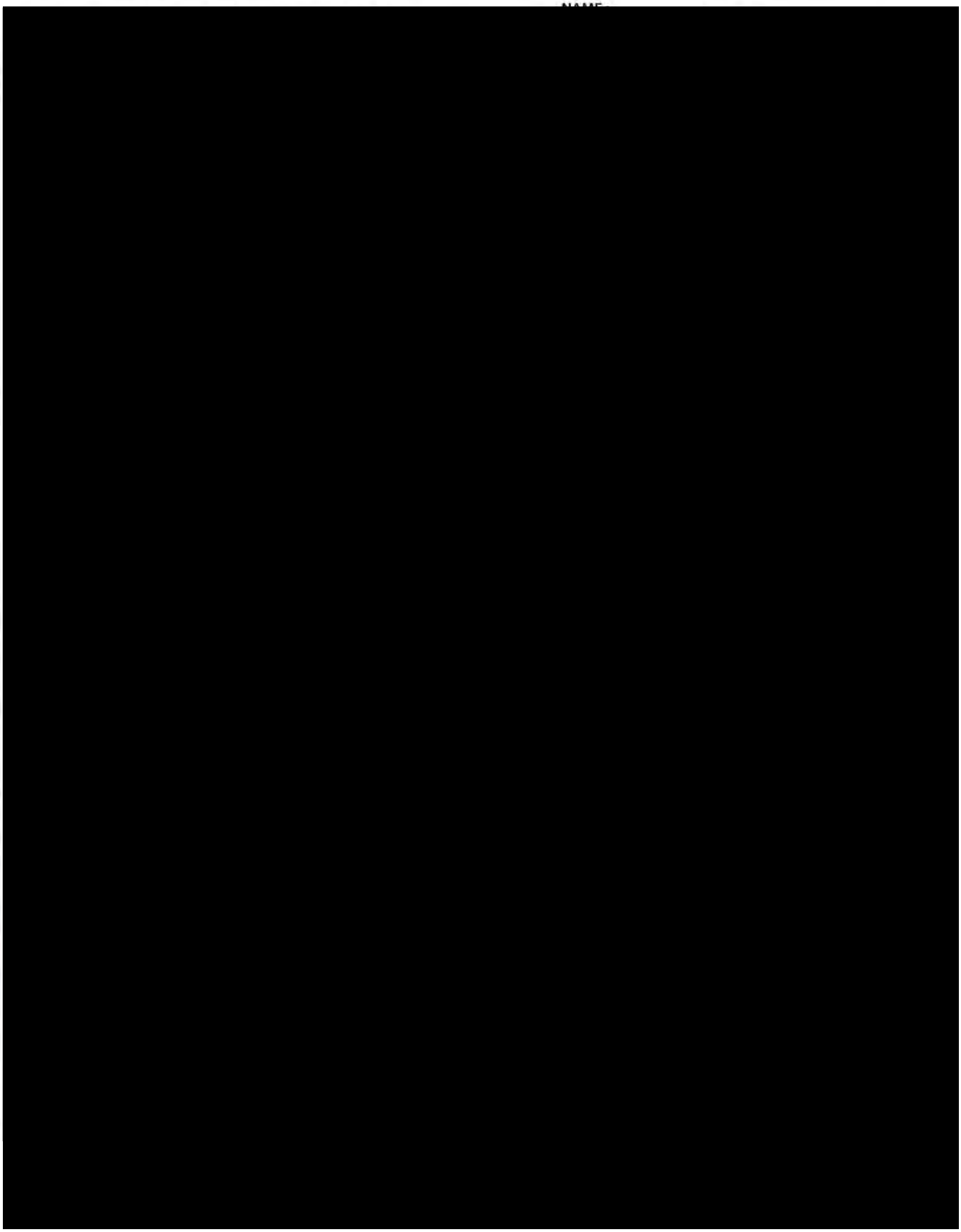

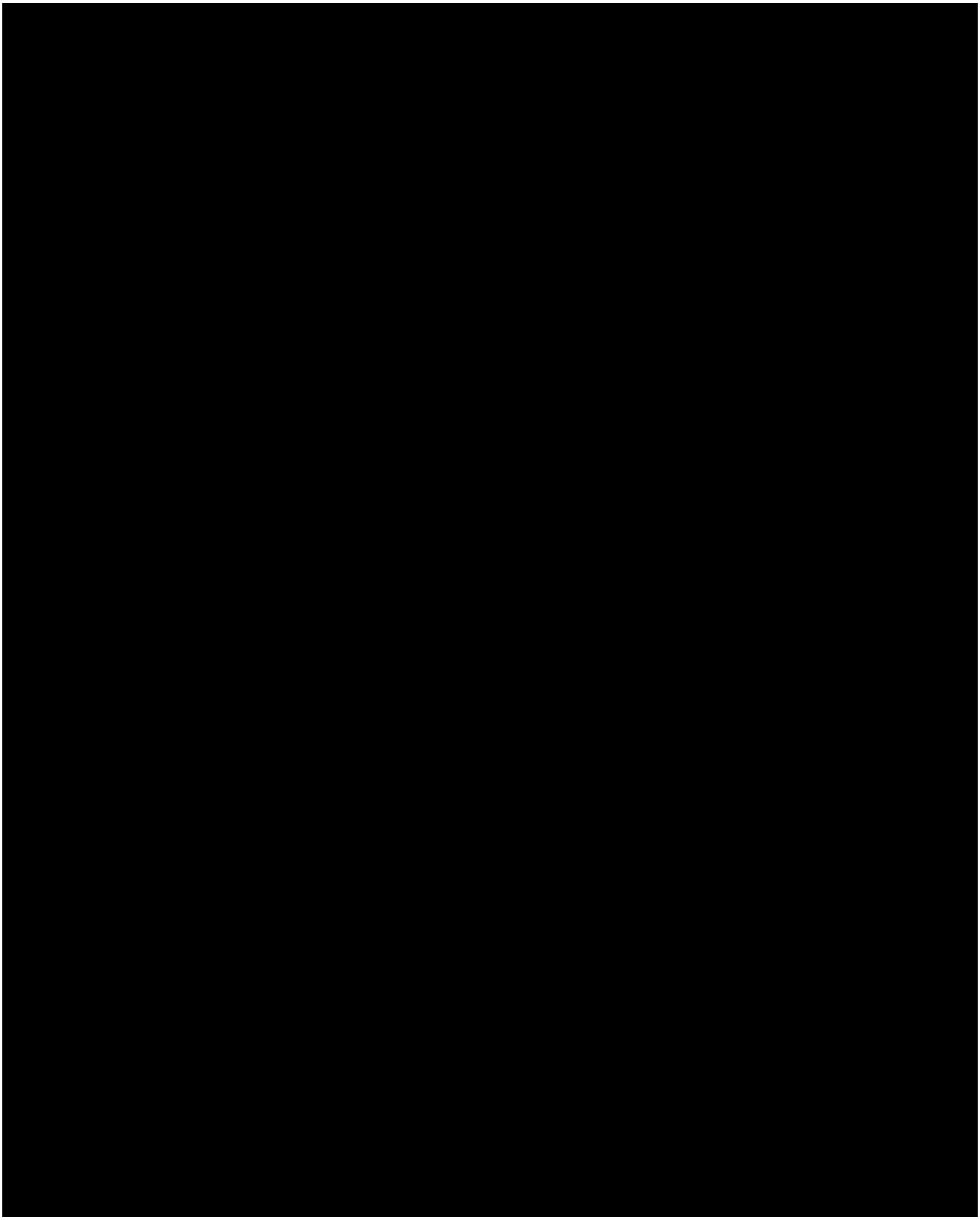

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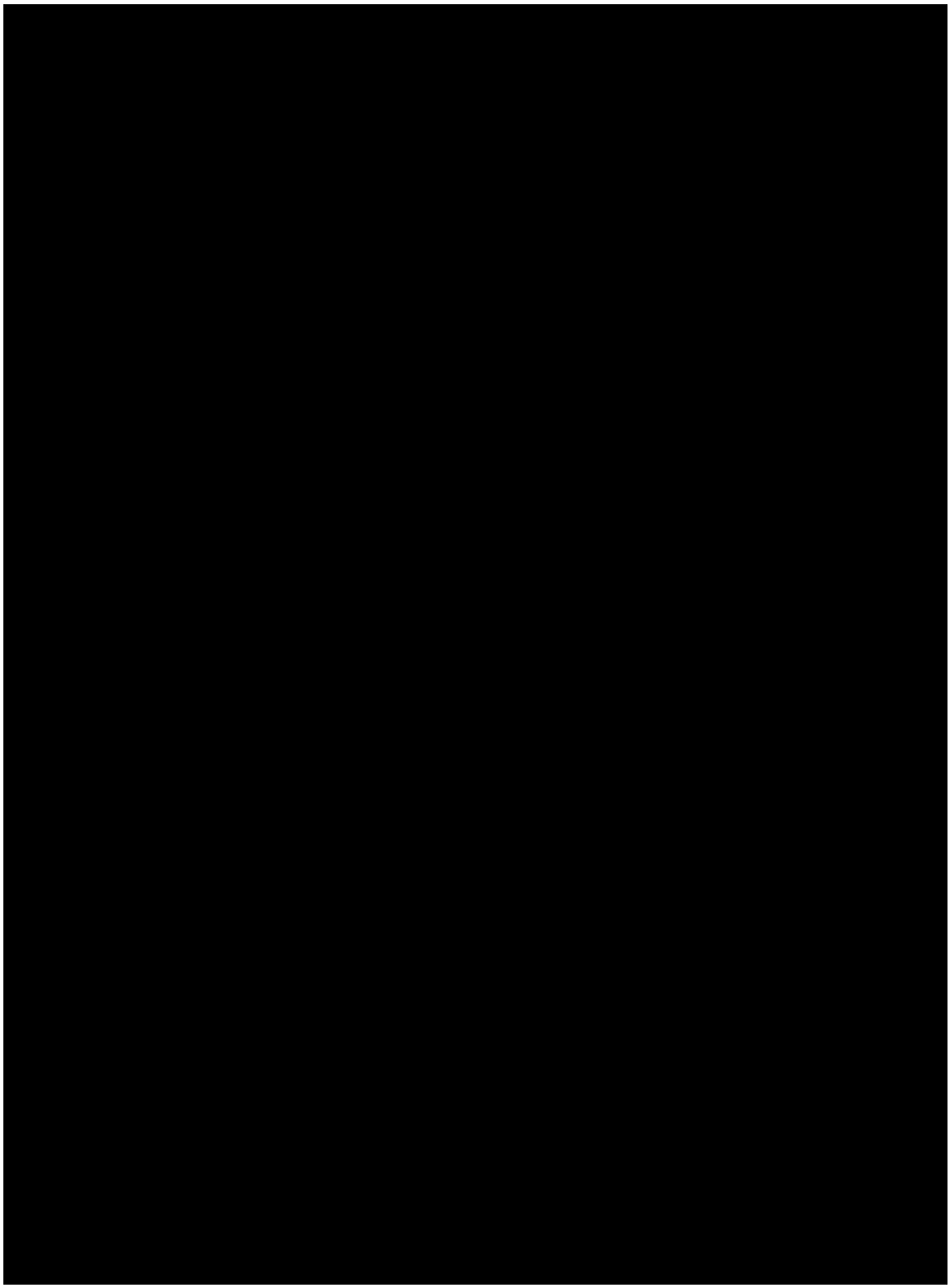


Appendix 13: Strong CYP2D6 Inhibitors

- Bupropion
- Fluoxetine
- Paroxetine

The maximum total daily dose of SD-809 for subjects with body weight less than 100 kg receiving any of the above strong CYP2D6 inhibitors is 36 mg per day. For subjects with body weight of 100 kg or more, receiving any of the above strong CYP2D6 inhibitors, the maximum total daily dose of SD-809 is 42 mg per day.

Appendix 14: Prohibited or Restricted QT Prolonging Drugs

Generic	Brand Name	Class/Clinical Use	Prohibited or Restricted	Note
Amiodarone	Cordarone®, Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	Prohibited	
Azithromycin	Zithromax®	Antibiotic / bacterial infection	Prohibited	
Bepridil	Vascor®	Anti-anginal / heart pain	Prohibited	
Chloroquine	Aralen®	Anti-malarial / malaria infection	Prohibited	
Citalopram	Celexa®	Anti-depressant / depression	Restricted	See Appendix 16 for dosing information
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	Prohibited	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Domperidone	Motilium®	Anti-nausea / nausea	Prohibited	Not available in U.S.
Droperidol	Inapsine®	Sedative; Anti-nausea/anesthesia adjunct, nausea	Prohibited	
Erythromycin	E.E.S.®, Erythrocin®	Antibiotic; GI stimulant; GI motility	Prohibited	
Escitalopram	Lexapro®, Cipralex®	Anti-depressant / Anxiety disorders	Restricted	See Appendix 16 for dosing information
Flecainide	Tambocor®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Halofantrine	Halfan®	Anti-malarial / malaria infection	Prohibited	
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Levomethadyl	Orlaam®	Opiate agonist/pain control, narcotic dependence	Prohibited	Not available in U.S.
Methadone	Dolophine®	Opiate agonist/pain control, narcotic dependence	Prohibited	
Methadone	Methadose®	Opiate agonist/pain control, narcotic dependence	Prohibited	
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	Prohibited	
Pentamidine	NebuPent®, Pentam®	Anti-infective / pneumocystis pneumonia	Prohibited	
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia	Prohibited	Not available in U.S.
Procainamide	Pronestyl®, Procan®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Quinidine	Quinaglute, Cardioquin	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general / anesthesia	Prohibited	
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Prohibited	
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	Prohibited	Not available in U.S.
Thioridazine	Mellaril®	Antipsychotic	Prohibited	
Vandetanib	Caprelsa®	Anti-cancer / Thyroid cancer	Prohibited	
Vardenafil	Levitra®	Phosphodiesterase inhibitor / vasodilator	Prohibited	

Appendix 15: Dopamine Receptor Antagonists

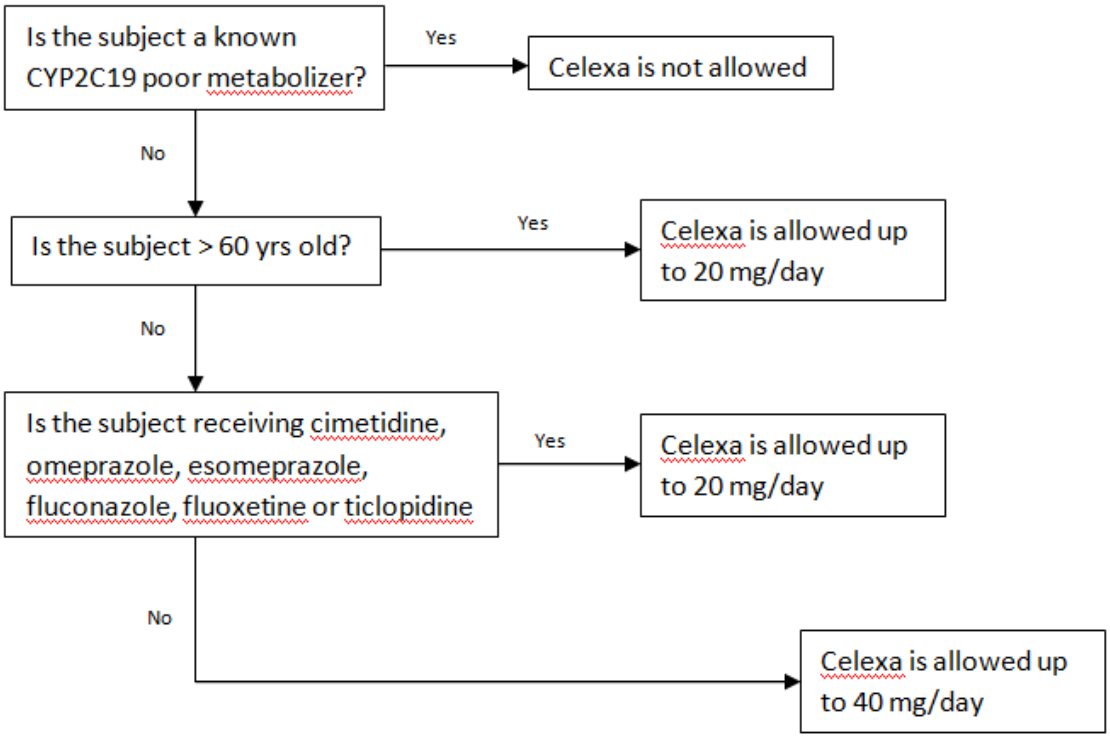
Typical/First Generation Antipsychotics	Typical Dosing	Atypical/Second Generation Antipsychotics	Typical Dosing
Chlorpromazine (Thorazine, Largactil)	30-800 mg/day (usual dose: 200-600 mg/day)	Aripiprazole (Abilify)	Usual dose:10-15 mg/day; up to 30 mg/day
Fluphenazine (Prolixin)	Initial: 2.5-10 mg/day; maintenance: 1-5 mg/day (up to 40 mg/day in some cases)	Asenapine Maleate (Saphris)	5 mg 2 times/day; up to 10 mg 2 times/day
Haloperidol (Haldol, Serenace)	0.5-5 mg/day 2-3 times/day; maximum: 30 mg/day	Clozapine (Clozaril)	Initial: 12.5 mg 1-2 times/day; target dose: 300-450 mg/day; maximum dose: 900 mg/day
Loxapine (Loxapac, Loxitane)	Initial: 10 mg 2 times/day; maintenance: 60-100 mg/day (maximum: 250 mg/day)	Iloperidone (Fanapt)	Initial: 1 mg 2 times/day; recommended range: 6-12 mg 2 times/day
Molindone (Moban; not available in US)	Initial: 50-75 mg/day; up to 225 mg/day	Lurasidone (Latuda)	Initial: 20 mg/day; maximum: 120 mg/day
Perphenazine (Trilafon)	Initial: 4-8 mg/day; up to 24 mg/day (up to 64 mg/day in hospitalized patients)	Olanzapine (Zyprexa)	Initial: 5-10 mg/day; maintenance: 10-20 mg/day (maximum: 30 mg/day for acute agitation)
Pimozide (Orap)	Initial: 1-2 mg/day; up to 10 mg/day (or 0.2 mg/kg/day)	Olanzapine/Fluoxetine (Symbyax)	Initial: 6 mg/25 mg per day; usual dose: 6-12 mg/25-50 mg per day
Thioridazine (Mellaril)	Prohibited	Paliperidone (Invega)	Usual dose: 6 mg/day; maximum: 12 mg/day
Thiothixene (Navane)	Initial: 2 mg 3 times/day; usual dose: 15 mg/day; maximum 60 mg/day for severe symptoms	Quetiapine (Seroquel)	Initial: 25 mg 2 times/day; Usual range: 150-750 mg/day
Trifluoperazine (Stelazine)	1-2 mg 2 times/day; up to 40 mg/day in hospitalized patients	Risperidone (Risperdal)	Initial: 2 mg 1-2 times/day; Recommended range: 4-8 mg/day
		Ziprasidone (Geodon)	Initial: 20 mg 2 times/day; maintenance: 20-100 mg 2 times/day
Other Agents			
Metaclopramide (Reglan)	10 mg 4 times/day		
Prochlorperazine (Compazine)	5-10 mg, 3-4 times/day; (usual maximum: 40 mg/day)		
Promethazine (Phenergan) containing compounds	12.5-50 mg/dose every 4-6 hours		

Appendix 16: Citalopram and Escitalopram Dosing Information

Citalopram (Celexa) is allowed with the following restrictions:

a) If the subject is a known CYP2C19 poor metabolizer, Celexa is not allowed.
b) If the subject is > 60 years old **or** is receiving cimetidine, omeprazole, esomeprazole, fluconazole, fluoxetine or ticlopidine, the maximum allowed dose is 20 mg/day.
c) If the subject is ≤ 60 years old and is not receiving any of the medications in (b) above, the maximum allowed dose is 40 mg.

The following flowchart may be used to determine the maximum allowable dose of Celexa:



Escitalopram (Lexapro or Cipralex) is allowed with the following restrictions:

Age	Maximum daily dose
< 65 years	20 mg
≥ 65 years	10 mg

Appendix 17: Protocol Summary of Changes, Original Protocol (Dated 24 March 2014) to Amendment 01 (Dated 28 May 2014)

Section	Original Protocol, dated 24 March 2014	Amendment 01, dated 28 May 2014	Reason for Change
Study Contacts, Medical Monitor	[redacted]	[redacted]	Update
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	2. Subject has received any of the following medications within 30 days of Baseline: • Reserpine, α-methyl-p-tyrosine (AMPT), anticholinergics, amantadine, or memantine • Metoclopraomide, stimulants, or monoamine oxidase inhibitors (MAOI)	2. Subject has received any of the following medications within 30 days of Baseline: • Reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Baseline), anticholinergics, amantadine, or memantine • Metoclopramide, stimulants, or monoamine oxidase inhibitors (MAOIs) • Levodopa or dopamine agonists	Botulinum toxin may confound assessments of the dyskinesia; correct inconsistency between exclusion criteria and prohibited concomitant medications
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18) and received study drug within 30 days (or 5 drug half-lives) of Screening, whichever is longer	15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer	Correct inconsistency between exclusion criteria and prohibited concomitant medications
Section 3, Investigational Plan	The study will be conducted at approximately 30 centers in the U.S., Canada, and possibly other regions.	The study will be conducted at approximately 30 centers in the U.S. and possibly other regions.	Clarification
Section 6.9.1, Concomitant Medications	**Prohibited Concomitant Medications** The following products should not be used within 4 weeks of Screening and throughout the study: • Metoclopromide • MAO Inhibitors • Levodopa or dopamine agonists • Reserpine • Amantadine • Memantine	**Prohibited Concomitant Medications** The following products should not be used within 30 days of Baseline (unless noted below) and throughout the study: • Tetrabenazine (within 7 days of Baseline) • AMPT • Metoclopromide • MAOIs • Levodopa or dopamine agonists • Reserpine • Anticholinergics • Amantadine • Memantine • Botulinum toxin (within 3 months of Screening) • Any investigational drug	Correct inconsistency between exclusion criteria and prohibited concomitant medications

Section	Original Protocol, dated 24 March 2014	Amendment 01, dated 28 May 2014	Reason for Change
Section 6.9.1, Concomitant Medications	*No text*	After 3 months, changes in psychoactive medications are allowed if approved by the Investigator. Any changes in concomitant medications must be documented in the eCRF.	Clarification
Section 8, Statistical Procedures and Data Analysis	Summary statistics will be provided by treatment.	Summary statistics will be provided by prior treatment (in Study SD-809-C-18) and for the overall population.	Clarification
Section 8.3, Safety Analysis	Descriptive statistics of change-from-baseline will use the Baseline from Study SD-809-C-18 (C-18 Baseline) and the Baseline from the present study (C-20 Baseline), as appropriate, and will be specified in the Statistical Analysis Plan.	Descriptive statistics of change-from-baseline will use the Baseline from the present study (SD-809-C-20 Baseline).	Clarification
Appendix 2, Abnormal Involuntary Movement Scale (AIMS)	*No Text*	**Scoring Criteria for Items 1 through 7**	Clarification
Appendix 2, Abnormal Involuntary Movement Scale (AIMS)	**Complete Examination Procedures before making ratings.** **Movement Ratings:** **Rate highest severity observed in category I, II, III**	**Complete Examination Procedures before making ratings.** **Rate highest severity observed in category I, II, III**	Clarification
Appendix 2, Abnormal Involuntary Movement Scale (AIMS)	**8. Severity of abnormal movements**	**8. Severity of abnormal movements** None, normal = 0 Minimal = 1 Mild = 2 Moderate = 3 Severe = 4	Clarification
Appendix 2, Abnormal Involuntary Movement Scale (AIMS)	**9. Incapacitation due to abnormal movements**	**9. Incapacitation due to abnormal movements** None, normal = 0 Minimal = 1 Mild = 2 Moderate = 3 Severe = 4	Clarification

Section	Original Protocol, dated 24 March 2014	Amendment 01, dated 28 May 2014	Reason for Change
Appendix 6, Unified Parkinson's Disease Rating Scale (UPDRS) Part III: Motor Examination		*Updated numbers of UPDRS to begin at 18 to better match Part III (Motor Examination) of the UPDRS.*	Clarification
Appendix 17, Protocol Summary of Changes, Original Protocol (dated 24 March 2014) to Amendment 01 (dated 28 May 2014)	*No Text*	*Addition of Appendix*	Summarize changes in Amendment 01
Global	investigational product	study drug	Clarification
Global		*Dates, section numbers, and tables of contents updated; typos and minor errors corrected*	Clarification

Appendix 18: Protocol Summary of Changes, Amendment 01 (dated 28 May 2014) to Amendment 02 (dated 08 July 2014)

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Global	dutetrabenazine	deutetrabenazine	Change in generic name
Cover Page	*No text*	EUDRACT No.: 2014-001891-73	Addition of EUDRACT number for European study sites
Study Contacts	[redacted]	[redacted]	Administrative change
Protocol Synopsis, Study Design	This is an open-label, single-arm study in which subjects with moderate to severe TD who have successfully completed the SD-809-C-18 study will be invited to participate. Informed consent/assent will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's SD-809-C-18 Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit.	This is an open-label, single-arm study in which subjects with moderate to severe TD who have successfully completed a parent study (SD-809-C-18 study or any other controlled study of SD-809 for the treatment of moderate to severe TD) will be invited to participate. Informed consent/assent will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Protocol Synopsis, Study Design	Subjects who have successfully completed Study SD-809-C-18 may be eligible to enroll into this study after they complete a 1-week washout period and Week 13 evaluation from Study SD-809-C-18. To reduce subject burden, after obtaining informed consent/assent, some data collected in Study SD-809-C-18 will be used in Study SD-809-C-20 and will provide some of the baseline data for Study SD-809-C-20 (see Schedule of Events). In addition to assessments completed for the SD-809-C-18 Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit.	Subjects who have successfully completed a parent study may be eligible to enroll into this study after they complete a 1-week washout period and the final evaluation in the parent study. To reduce subject burden, after obtaining informed consent/assent, some data collected in the parent study will be used in Study SD-809-C-20 and will provide some of the baseline data for Study SD-809-C-20 (see Schedule of Events). For example, in addition to assessments completed for the SD-809-C-18 Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Protocol Synopsis, Study Design	**Titration Period (up to 6 weeks):** As subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the SD-809-C-18 study, they will undergo SD-809 dose titration in this study.	**Titration Period (up to 6 weeks):** As subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo SD-809 dose titration in this study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Protocol Synopsis, Dose Regimen	Once the Investigator determines that a stable dose has been reached, SD-809 will be supplied in 30-count bottles.	During long-term treatment, SD-809 will be supplied in 30-count bottles.	Clarification
Protocol Synopsis, Dose Regimen	• The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the SD-809-C-18 trial. Prior treatment assignment from Study SD-809-C-18 will remain blinded.	• The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the parent trial. Prior treatment assignment from the parent trial will remain blinded.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Protocol Synopsis, Sample Size	Approximately 80 subjects (eligible subjects who completed SD-809-C-18 may enroll)	Approximately 260 subjects (eligible subjects who completed SD-809-C-18 or any other controlled study of SD-809 for treatment of moderate to severe TD may enroll)	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Protocol Synopsis, Inclusion Criteria Section 4.2, Inclusion Criteria	2. Subject has successfully completed Study SD-809-C-18[a]	2. Subject has successfully completed [a] Study SD-809-C-18 or another controlled study of SD-809 for treatment of moderate to severe TD	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Footnotes “a” and “d”	Successful completion of Study SD-809-C-18 is defined as (1) study participation through Week 13 (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator, and (3) the subject has no ongoing AEs that are serious or severe in intensity or are expected to interfere with safety evaluations in this study.	Successful completion is defined as (1) study participation through Week 13 (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator, and (3) the subject has no ongoing AEs that are serious or severe in intensity or are expected to interfere with safety evaluations in this study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	2. Subject has received any of the following medications within 30 days of Screening or Baseline: a. Tetrabenazine, reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Screening), anticholinergics, amantadine, or memantine b. Metoclopramide, stimulants, or monoamine oxidase inhibitors (MAOIs) • Levodopa or dopamine agonists	2. Subject has received any of the following medications within 30 days of Screening or Baseline: • Tetrabenazine, reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Screening), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden) • Metoclopramide, promethazine, and prochlorperazine • Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc.), or monoamine oxidase inhibitors (MAOIs) • Levodopa or dopamine agonists	Modified to better reflect medications likely to have significant interactions with SD-809 and/or directly oppose the effects of SD-809 based on known mechanism of action. In addition, additional guidance on specific anticholinergics and stimulants considered exclusionary is provided
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	6. Subject has history of any of the following within 5 years of Baseline: • Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on C-SSRS), irrespective of level of ambivalence at the time of suicidal thought • Previous preparatory acts to commit suicide or suicidal behavior • A previous actual, interrupted or aborted suicide attempt	6. Subject has history of any of the following within 6 months of Baseline: • Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on C-SSRS), irrespective of level of ambivalence at the time of suicidal thought • Previous preparatory acts to commit suicide or suicidal behavior • A previous actual, interrupted or aborted suicide attempt	Time frame modified from 5 years to 6 months, as this time frame is considered more clinically relevant to accurately determine eligibility for this trial.
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	14. Subject has known allergy to any of the components of study drug	14. Subject has known allergy to tetrabenazine or to any of the components of SD-809.	Clarification

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer.	15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18 or any other eligible SD-809 parent study) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Protocol Synopsis, Statistics	Safety data will be summarized descriptively for the overall population and based on prior treatment (SD-809 or placebo) in Study SD-809-C-18.	Safety data will be summarized descriptively for the overall population and based on prior treatment (SD-809 or placebo) in the parent study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Protocol Synopsis, Statistics	Descriptive statistics of change-from-baseline will utilize the Baseline from Study SD-809-C-18 (C-18 Baseline) and the Baseline from the present study (C-20 Baseline), as appropriate, and will be specified in the Statistical Analysis Plan.	Descriptive statistics of change-from-baseline will use the Baseline from the present study and will be specified in the Statistical Analysis Plan.	Correct inconsistency between synopsis and main text
Protocol Synopsis, Statistics	Descriptive statistics will be used to summarize efficacy measures for the overall population and based on prior treatment (SD-809 or placebo) from Study SD-809-C-18.	Descriptive statistics will be used to summarize efficacy measures for the overall population and based on prior treatment (SD-809 or placebo) in the parent study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Schedule of Events (Global change)	Study SD-809-C-18	Parent study	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Schedule of Events	*MoCA© at Week 4 and Week 55 visits.*	*MoCA© deleted at Week 4 and Week 55*	Reduce subject burden and decrease potential for practice effects.
Schedule of Events	*Return Study Drug at Visit 54*	*Procedure deleted*	Remove duplication of assessment of study drug accountability/compliance

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Schedule of Events Footnote 7	Subjects who experience an SAE should have a single blood sample collected for metabolites of SD-809 within 48 hours of SAE, if possible.	Subjects who experience an SAE should have a blood sample collected for pharmacokinetic assessment as soon as possible after the SAE and within 48 hours of the last dose of study drug, if possible.	Clarification
Protocol Approval Page	*No text*	*Added signature for Principal Investigator*	Added Investigator signatures for European study sites.
Section 3, Investigational Plan	Approximately 80 subjects who have successfully completed the Phase 2/3 SD-809-C-18 efficacy study will be enrolled.	Approximately 260 subjects who have successfully completed a parent study (Phase 2/3 SD-809-C-18 efficacy study or any other SD-809 study for treatment of moderate to severe TD) will be enrolled.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 3.1, Study Design	This is an open-label, single-arm study in which subjects with moderate to severe drug-induced TD who have successfully completed the SD-809-C-18 efficacy study will be invited to participate. Successful completion of Study SD-809-C-18 is defined as (1) study participation through Week 13 (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator and (3) the subject has no ongoing AEs that that are serious (SAE)[c], severe in intensity or are expected to interfere with their participation in this study. Informed consent/assent will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's SD-809-C-18 Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Subjects who have successfully completed Study SD-809-C-18 may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 evaluation of Study SD-809-C-18. To reduce subject burden, after obtaining informed consent/assent, some data collected in the SD-809-C-18 study will be used in the SD-809-C-20 study and will provide some of the baseline data for SD-809-C-20 (see	This is an open-label, single-arm study in which subjects with moderate to severe drug-induced TD who have successfully completed a parent study will be invited to participate. Successful completion of a parent study is defined as (1) study participation through Week 13 (2) the subject has generally been compliant with study drug and procedures, in the opinion of the investigator and (3) the subject has no ongoing AEs that that are serious (SAE)[c], severe in intensity or are expected to interfere with their participation in this study. Informed consent/assent will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Subjects who have successfully completed a parent study may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 evaluation of the parent study. To reduce subject burden, after obtaining informed consent/assent, some data collected in the parent study will be used in the SD-809-C-20 study and will provide some of the baseline data for SD-809-C-20 (see Schedule of Events). In addition to assessments completed for the parent study Week 13 visit,	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
	Schedule of Events). In addition to assessments completed for the SD-809-C-18 Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit. **Titration Period (up to 6 weeks):** As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the SD-809-C-18 study, they will undergo titration on SD-809 in this study.	evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit. **Titration Period (up to 6 weeks):** As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo titration on SD-809 in this study.	
Section 3.2, Rationale for Study Design	Subjects who successfully complete the placebo-controlled efficacy study (SD-809-C-18) will be eligible to enroll.	Subjects who successfully complete a placebo-controlled efficacy study (SD-809-C-18 or any other controlled study of SD-809 as treatment for moderate to severe TD) will be eligible to enroll.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 3.2, Rationale for Study Design	The present investigation is an open-label safety study of up to 54 weeks treatment with SD-809 at a pharmacologically active dose and will enroll subjects with drug-induced dyskinesia associated with TD who were either previously exposed to SD-809 or placebo (from Study SD-809-C-18). The US prescribing information for tetrabenazine indicates that CYP2D6 genotyping should be performed at doses higher than 50 mg, although genotyping is often not performed in clinical practice as the drug is titrated. In the present study, CYP2D6 genotyping will have been performed in a blinded manner in the previous study (SD-809-C-18) to allow evaluation of the effect of phenotype on safety parameters at the conclusion of the study.	The present investigation is an open-label safety study of up to 54 weeks treatment with SD-809 at a pharmacologically active dose and will enroll subjects with drug-induced dyskinesia associated with TD who were previously exposed to either SD-809 or placebo in a parent study. The US prescribing information for tetrabenazine indicates that CYP2D6 genotyping should be performed at doses higher than 50 mg, although genotyping is often not performed in clinical practice as the drug is titrated. In the present study, CYP2D6 genotyping will have been performed in a blinded manner in the parent study to allow evaluation of the effect of phenotype on safety parameters at the conclusion of the study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 4.1, Population Characteristics	Male and female adult subjects with TD who have successfully completed the SD-809-C-18 efficacy study and meet eligibility criteria will be enrolled.	Male and female adult subjects with TD who have successfully completed the parent study (Study SD-809-C-18 or any other controlled study of SD-809 for treatment of moderate to severe TD) efficacy study and meet eligibility criteria will be enrolled.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Section 5.1, Study Drug	**Once the Investigator determines that a stable dose has been reached, SD-809 will be supplied in 30 count bottles and labeled according to applicable regulatory guidelines.**	**During long-term treatment, SD-809 will be supplied in 30 count bottles and labeled according to applicable regulatory guidelines.**	Clarification
Section 5.2.1, General Guidelines	• The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the SD-809-C-18 trial. Prior treatment assignment from Study SD-809-C-18 will remain blinded.	• The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the parent study. Prior treatment assignment from the parent study will remain blinded.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 6.1.1	**6.1.1 Prior Data from Study SD-809-C-18**	**6.1.1 Prior Data from the Parent Study**	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 6.1.1, Prior Data from the Parent Study	*See Schedule of Events for data to be imported from SD-809-C-18 after informed consent/assent.* Subjects who have successfully completed Study SD-809-C-18 may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 (visit window up to 10 days) evaluation of Study SD-809-C-18. To reduce subject burden, after obtaining informed consent/assent, some data collected in the SD-809-C-18 study will be used in the SD-809-C-20 study and provide some of the baseline data for SD-809-C-20 (see Schedule of Events). In addition to assessments completed for the SD-809-C-18 Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit. All subjects participating in SD-809-C-20 are expected to rollover to SD-809-C-20 at the Week 13 visit of SD-809-C-18.	*See Schedule of Events for data to be imported from the parent study after informed consent/assent.* Subjects who have successfully completed a parent study may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 (visit window up to 10 days) evaluation of the parent study. To reduce subject burden, after obtaining informed consent/assent, some data collected in the parent study will be used in the SD-809-C-20 study and provide some of the baseline data for SD-809-C-20 (see Schedule of Events). In addition to assessments completed for the parent study Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit. All subjects participating in SD-809-C-20 are expected to rollover to SD-809-C-20 at the Week 13 visit of the parent study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Section 6.2, Dose Adjustment Period	As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week after completion of the SD-809-C-18 study, they will undergo titration on SD-809 in this study.	As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week after completion of the parent study, they will undergo titration on SD-809 in this study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 6.4.1, Clinic Visit (Week 55 ± 3 days)	• MoCA©	*Text deleted.*	Reduce subject burden and decrease potential for practice effects.
Section 6.7.1, Demographic and Medical History	The subject's gender, date of birth, race, ethnic origin, and medical and surgical history will be transferred from data collected in Study SD-809-C-18.	The subject's gender, year of birth, age, race, ethnic origin, and medical and surgical history will be transferred from data collected in the parent study.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 6.7.6, Laboratory Tests	**Screening Labs**	**Labs for Screening Purposes**	Clarification that these laboratory evaluations are for screening purposes, but may occur at a visit other than Screening
Section 6.7.6, Laboratory Tests	• CAG repeat (blinded)	*Text deleted*	CAG repeat evaluation not relevant to this study
Section 6.7.7, 12-lead Electrocardio-gram	12-lead ECGs to assess safety will be recorded according to the Schedule of Events and interpreted by a cardiologist. Heart rate and ECG intervals (PR, QRS, QT, and QTcF) and clinical interpretation will be assessed by the cardiologist and recorded in the CRF.	12-lead ECGs to assess safety will be collected according to the Schedule of Events. Heart rate and ECG intervals (PR, QRS, QT, and QTcF) and clinical interpretation will be assessed by the central reader.	Clarification
Section 6.8, Pharmaco-kinetic Evaluations	Subjects experiencing an SAE should have a single blood sample collected as soon as possible after the SAE and within 48 hours for the pharmacokinetics of α- and β- HTBZ, if possible. The date and time of the last dose of study drug should be recorded along with the date and time of the sample collection.	Subjects experiencing an SAE should have a single blood sample collected as soon as possible after the SAE and within 48 hours of the last dose of study drug for the pharmacokinetic assessment of α- and β- HTBZ, if possible. The date and time of the last dose of study drug should be recorded along with the date and time of the sample collection.	Clarification

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Section 6.9.1, Concomitant Medications	**Prohibited Concomitant Medications** The following products should not be used within 30 days of Baseline (unless noted below) and throughout the study: • Tetrabenazine (within 7 days of baseline) • AMPT • Metoclopromide • MAOIs • Levodopa or dopamine agonists • Reserpine • Anticholinergics • Amantadine • Memantine • Botulinum toxin (within 3 months of Screening) • Any investigational drug	**Prohibited Concomitant Medications** The following products should not be used within 30 days of Baseline (unless noted below) and throughout the study: • Tetrabenazine (within 7 days of Baseline) • AMPT • Metoclopromide, promethazine, and prochlorperazine • Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc.) • MAOIs • Levodopa or dopamine agonists • Reserpine • Medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden) • Botulinum toxin (within 3 months of Screening) • Any investigational drug	Modified to better reflect medications likely to have significant interactions with SD-809 and/or directly oppose the effects of SD-809 based on known mechanism of action. In addition, additional guidance on specific anticholinergics and stimulants considered exclusionary is provided.
Section 6.13, Study Termination	The Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.	The Investigator reserves the right to discontinue the study at their site for safety reasons at any time in collaboration with the Sponsor.	Clarification
Section 7.4.2, Regulatory Reporting Requirements for SAEs	The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures describe above.	The Investigator must promptly (within 24 hours of awareness) report all SAEs to the Sponsor (or designee) in accordance with the procedures describe above.	Clarification
Section 8, Statistical Procedures and Data Analysis	Summary statistics will be provided by prior treatment (in Study SD-809-C-18) and for the overall population.	Summary statistics will be provided by prior treatment (in parent study) and for the overall population.	Subjects previously participating in another study of SD-809 for the treatment of moderate to severe TD will be allowed to participate in Study SD-809-C-20.
Section 8.3, Safety Analysis	Safety data will be summarized descriptively for the overall population and based on prior treatment (SD-809 or placebo).	Safety data will be summarized descriptively for the overall population and based on prior treatment (SD-809 or placebo) in the parent study.	Clarification

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Section 9.4.1, Safety Monitoring Committee (SMC)	**9.4.1 Safety Monitoring Committee (SMC)** An independent Safety Monitoring committee (SMC) will be established prior to study start, with an appropriate charter to direct decisions and communications, maintain a firewall to preserve the blinding and integrity of the study, and monitor the trial safety results at intervals throughout the study. The SMC will be comprised of at least two clinicians, at least one of which is experienced in treating patients with movement disorders such as TD, and a statistician not otherwise associated with the trial. The main purpose of the SMC will be to protect the interests of the subjects enrolled in the trial. The SMC will determine the data necessary for monitoring and the intervals for formal review and discussion (e.g., after certain percentage of enrolled subjects complete treatment), and this information will be specified in the SMC charter. The SMC will make recommendations to the Sponsor as to whether the trial should continue as planned or whether modifications should be made to safety monitoring. Minutes will be kept of all meetings but those referring to unblinded data will not be made available outside of the SMC until the trial is complete. The final decision on whether the protocol should be amended or the study should be terminated will be the responsibility of the Sponsor. Any decision to stop will be communicated to investigators and regulatory agencies.	*Text deleted*	Safety monitoring committee not required for this open-label study.
Appendix 1, Site Investigator Signature Page	**I have read and understand Protocol SD-809-C-20 in its entirety and I agree to all aspects.**	**I have read and understand Protocol SD-809-C-20 Amendment 02 in its entirety and I agree to all aspects.**	Clarification
Appendix 1, Site Investigator Signature Page	**Principal Investigator**	**Investigator**	Clarification

Section	Amendment 01, dated 28 May 2014	Amendment 02, dated 08 July 2014	Reason for Change
Appendix 18, Protocol Summary of Changes, Protocol Amendment 01 (dated 28 May 2014) to Amendment 02 (dated 08 July 2014) to	*No Text*	*Addition of Appendix 18*	Summarize changes in Amendment 02
Global	*Not applicable*	*Dates, section numbers, and tables of contents updated; typos and minor errors corrected*	Clarification

Appendix 19: Protocol Summary of Changes, Amendment 02 (dated 08 July 2014) to Amendment 03 (dated 14-Oct-2015)

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
Study Contacts	[redacted]	[redacted]	Administrative change
Protocol Synopsis, No. Sites Section 3, Investigational Plan	Approximately 30	Approximately 80	Update to number of study sites
Protocol Synopsis, Study Population	Male and female adult subjects with moderate to severe drug-induced TD who have successfully completed the SD-809-C-18 efficacy study (approximately 80 subjects) will be enrolled.	Male and female adult subjects with moderate to severe drug-induced TD who have successfully completed a previous placebo-controlled efficacy study of SD-809 for the treatment of TD with the Sponsor will be enrolled.	Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled
Protocol Synopsis, Study Population	This is an open-label, single-arm study in which subjects with moderate to severe TD who have successfully completed a parent study (SD-809-C-18 study or any other controlled study of SD-809 for the treatment of moderate to severe TD) will be invited to participate.	This is an open-label, single-arm study in which subjects with moderate to severe TD who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for the treatment of moderate to severe TD) will be invited to participate.	Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
Protocol Synopsis, Study Design Section 3.1, Study Design Section 6.3, Long-Term Treatment Period	**Long-Term Treatment Period (up to 52 weeks):** During long-term treatment, subjects will continue titration through Week 6. During this period, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Weeks 4, 6, 15, 28, 41, and 54 for evaluation of safety and dyskinesia control. Subjects who have not achieved a dose level that adequately controls dyskinesia and is well tolerated by the Week 6 visit should have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Interactions with the clinical site for dose adjustment should alternate between telephone contacts and clinic visits. During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and only in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's (if appropriate) reports of AEs and dyskinesia control, as well as information from rating scales and safety evaluations, when available.	**Long-Term Treatment Period (up to 2 years):** During long-term treatment, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a dose level that adequately controls dyskinesia and is well tolerated by the Week 6 visit should have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Interactions with the clinical site for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 106 (i.e., after 2 years of Long-Term Treatment Period). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and only in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's (if appropriate) reports of AEs and dyskinesia control, as well as information from rating scales, and safety evaluations, when available. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers.	Extension of Long-Term Treatment Period from 1 year to 2 years and addition of clinic visits during the extension
Protocol Synopsis, Study Design	**Post-Treatment Safety Follow Up:** All subjects will discontinue study drug at the Week 54 visit and return for their final clinic visit at Week 55 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout period, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 58, 4 weeks after their last dose of study drug, to evaluate AEs and concomitant medication usage.	**Post-Treatment Safety Follow-up:** All subjects will discontinue study drug at the Week 106 visit and return for their final clinic visit at Week 107 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout period, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 110, 4 weeks after their last dose of study drug, to evaluate AEs and concomitant medication usage.	Extension of Long-Term Treatment Period from 1 year to 2 years

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
Protocol Synopsis, Sample Size	Approximately 260 subjects (eligible subjects who completed SD-809-C-18 or another controlled study of SD-809 for treatment of moderate to severe TD may enroll)	Approximately 330 subjects (eligible subjects who completed a previous controlled study of SD-809 for treatment of moderate to severe TD) may enroll.	Update to number of subjects based on current enrollment for Study SD-809-C-18 and Study SD-809-C-23
Protocol Synopsis, Inclusion Criteria Section 4.2, Inclusion Criteria	2. Subject has successfully completed Study SD-809-C-18 or any other controlled study of SD-809 for treatment of moderate to severe TD	2. Subject has successfully completed Study SD-809-C-18, SD-809-C-23, or any other controlled study of SD-809 for treatment of moderate to severe TD.	Clarification that subjects who complete any eligible parent study of SD-809 for TD, including Study SD-809-C-23, may be enrolled
Protocol Synopsis, Inclusion Criteria Section 4.2, Inclusion Criteria	5. For subjects with underlying psychiatric illness ... • Subject has a mental health provider who is aware of the subject's participation in the trial and does not anticipate any changes to the subject's treatment regimen (drug, dose, frequency) in the next 3 months.	5. For subjects with underlying psychiatric illness ... • Subject has a health care provider who is aware of the subject's participation in the trial and does not anticipate any changes to the subject's treatment regimen (drug, dose, frequency) in the next 3 months.	Clarification
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	6. Subject has a history of any of the following within 6 months of Baseline: • Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on the Columbia Suicide Severity Rating Scale [C-SSRS]), irrespective of level of ambivalence at the time of suicidal thought ...	6. Subject has a history of any of the following within 6 months of Screening: • Previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence at the time of suicidal thought ...	Clarification
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	12. Subject has evidence of hepatic impairment at Screening, as indicated by: ... • Prothrombin time >4 seconds prolonged. ...	12. Subject has evidence of hepatic impairment at Screening of the parent study, as indicated by: ... • Prothrombin time >17 seconds (i.e., prothrombin time prolonged >4 seconds over the ULN). ...	Clarification

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	13. Subject has evidence of significant renal impairment at Screening, indicated by...	13. Subject has evidence of significant renal impairment at Screening of the parent study, indicated by...	Clarification
Protocol Synopsis, Exclusion Criteria Section 4.3, Exclusion Criteria	15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18 or any other eligible SD-809 parent study) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer.	15. Subject has participated in an investigational drug or device trial (other than Study SD-809-C-18, Study SD-809-C-23, or any other eligible SD-809 parent study) and received study drug within 30 days (or 5 drug half-lives) of Baseline, whichever is longer.	Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled
Protocol Synopsis, Efficacy Measures Section 8.5, Efficacy Measures	• The change in Abnormal Involuntary Movement Scale (AIMS) score (items 1 through 7) from Baseline of this study to end of long-term therapy (Week 54) as assessed by blinded central video rating. • The proportion of subjects who are a treatment success at the end of long-term therapy (Week 54), based on the Clinical Global Impression of Change (CGIC). A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study to end of long-term therapy. • Change in the modified Craniocervical Dystonia (CDQ-24) score from Baseline of this study to the end of long-term therapy (Week 54). • The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline of this study to the end of long term therapy (Week 54) • The proportion of subjects who are a treatment success at the end of long-term therapy (Week 54), based on the Patient Global Impression of Change (PGIC). A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study to end of long-term therapy. • The percent change in AIMS score from Baseline	• The change in Abnormal Involuntary Movement Scale (AIMS) score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by blinded central video rating. • The change in AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by the site rating. • The proportion of subjects who are a treatment success based on the Clinical Global Impression of Change (CGIC) at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study. • The change in the modified Craniocervical Dystonia (CDQ-24) score from Baseline of this study at each visit that this is measured. • The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline of this study at each visit that this is measured. • The proportion of subjects who are a treatment success based on the Patient Global Impression of Change (PGIC) at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study. • The percent change in AIMS score from Baseline of this study at each visit that this is measured.	Efficacy measures from throughout the study will now be analyzed, not just at the end of 1 year of long-term treatment

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
	of this study to the end of long term therapy (Week 54). • Based on the change in AIMS score from Baseline of this study to the end of long-term therapy (Week 54), as assessed by blinded central video rating, the cumulative proportion of responders ranging from a 10% improvement from Baseline to a 90% improvement from Baseline in steps of 10 percentage points.	• Based on the change in AIMS score from Baseline of this study at each visit that this is measured, as assessed by blinded central video rating, the cumulative proportion of responders ranging from a 10% improvement from Baseline to a 90% improvement from Baseline in steps of 10 percentage points.	
Schedule of Events	*Not applicable*	*Addition of quarterly clinic visits at Weeks 67, 80, 93, and 106/ET. Change of Follow-up Period clinic visit to Week 107 and telephone contact to Week 110.*	Extension of Long-Term Treatment Period from 1 year to 2 years and addition of clinic visits during the extension
Protocol Approval Page	[redacted]	[redacted]	Update of title and affiliation
Section 3, Investigational Plan	This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD over a 54-week period. Approximately 260 subjects who have successfully completed a parent study (Phase 2/3 SD-809-C-18 efficacy study or any other SD-809 study for treatment of moderate to severe TD) will be enrolled. The study will be conducted at approximately 30 centers in the U.S. and possibly other regions. The study is divided into a Screening Period, a Titration Period, a Long-Term Treatment Period, and a Post-Treatment Safety Follow-up Period. For subjects who complete the study, overall study participation will be up to 58 weeks.	This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD for up to 2 years (106 weeks). Approximately 330 subjects who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other SD-809 study for treatment of moderate to severe TD) will be enrolled. The study will be conducted at approximately 80 centers in the U.S., Europe, and possibly other regions. The study is divided into a Screening Period, a Titration Period, a Long-Term Treatment Period, and a Post-Treatment Safety Follow-up Period. For subjects who complete the study, overall study participation will be up to 110 weeks.	Extension of Long-Term Treatment Period from 1 year to 2 years Update to number of subjects Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled Update to number of study sites

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
Section 3.1, Study Design	**Titration Period (up to 6 weeks):** As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the SD-809-C-18 study, they will undergo titration on SD-809 in this study.	**Titration Period (up to 6 weeks):** As all subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo titration on SD-809 in this study.	Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled
Section 3.1, Study Design	**Post-Treatment Safety Follow Up:** All subjects will discontinue study drug at the Week 54 visit and return for their final clinic visit at Week 55 for evaluation of safety, dyskinesia control, and motor function. During this one week washout, subjects should not take prohibited concomitant medications. Between the Week 55 visit and the Week 58 telephone contact, concomitant medication use is per the discretion of the Investigator. Subjects will also have a follow-up telephone contact at Week 58, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage.	**Post-Treatment Safety Follow-up:** All subjects will discontinue study drug at the Week 106 visit and return for their final clinic visit at Week 107 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 110, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage. Between the Week 107 visit and the Week 110 telephone contact, concomitant medication use is per the discretion of the Investigator.	Extension of Long-Term Treatment Period from 1 year to 2 years
Section 3.2, Rationale for Study Design	Subjects who successfully complete a placebo-controlled efficacy study (SD-809-C-18 or any other controlled study of SD-809 as treatment for moderate to severe TD) will be eligible to enroll.	Subjects who successfully complete a placebo-controlled efficacy study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 as treatment for moderate to severe TD) will be eligible to enroll.	Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled
Section 3.2, Rationale for Study Design	The present investigation is an open-label safety study of up to 54 weeks of treatment with SD-809...	The present investigation is an open-label safety study of up to 106 weeks of treatment with SD-809...	Extension of Long-Term Treatment Period from 1 year to 2 years
Section 4.1, Population Characteristics	Male and female adult subjects with TD who have successfully completed the parent study (Study SD-809-C-18 or any other controlled study of SD-809 for treatment of moderate to severe TD) efficacy study and meet eligibility criteria will be enrolled.	Male and female adult subjects with TD who have successfully completed the parent efficacy study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for treatment of moderate to severe TD) and meet eligibility criteria will be enrolled.	Clarification that subjects who complete any eligible parent study of SD-809 for TD may be enrolled
Section 5, Study Treatment	The initial drug supply will be provided in the clinic at the Baseline visit.	The initial drug supply will be provided to the subject in the clinic at the Baseline visit.	Clarification
Section 5.2.2 (heading changed)	**Dosing in Long-Term Treatment (Weeks 3-54)**	**Dosing in Long-Term Treatment (Weeks 3 to 106)**	Extension of Long-Term Treatment

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
			Period from 1 year to 2 years
Section 6.1.1 (heading changed)	**Prior Data from Study SD-809-C-18**	**Prior Data from Subject's Parent Study**	Subjects who complete any eligible parent study of SD-809 for TD may be enrolled, and their prior data will then be used for this study
Section 6.1.2, Baseline Visit	Obtain informed consent or assent	Obtain or verify informed consent or assent	Clarification
Section 6.3, Long-Term Treatment Period	At the end of the Long-Term Treatment Period (Week 54), subjects will undergo a comprehensive evaluation, including physical and complete neurological exam, safety labs, 12-lead ECG, and performance of all rating scales.	At Weeks 28, 54, and 106, subjects will undergo a more comprehensive evaluation, including physical exam, complete neurological exam (Weeks 54 and 106 only), safety labs, 12-lead ECG, urine pregnancy test for women of childbearing potential, and performance of all rating scales.	Extension of Long-Term Treatment Period from 1 year to 2 years and addition of clinic visits during the extension
Section 6.3.2 (heading changed)	**Clinic Visits (Weeks 4, 6, 15, 28, and 41 [all ± 3 days])** ... • Brief physical examination (Week 28 only) ... • 12-lead ECG (Weeks 4, 6, and 41) • Clinical laboratory tests: serum chemistry, hematology, and urinalysis (Weeks 6 and 28) • Urine pregnancy test (women of child-bearing potential only; Week 28 only) • AIMS • Video recording of AIMS (Weeks 6, 15, 28, and 41) ... • MoCA© (Weeks 6, 15, 28, 41) • Modified CDQ-24 (Weeks 6, 15, 28, 41) • Next clinic visit and telephone contact (Week 4)	**Clinic Visits (Weeks 4, 6, 15, 41, 67, 80, and 93 [all ± 3 days])** ... • *Deleted bullet* ... • 12-lead ECG (Weeks 4, 6, and 41) • Clinical laboratory tests: serum chemistry, hematology, and urinalysis (Week 6 only) • *Deleted bullet* • AIMS • Video recording of AIMS (Weeks 6, 15, and 41) ... • MoCA© (Weeks 6, 15, 41, 67, 80, 93) • Modified CDQ-24 (Weeks 6, 15, 41) ... • Next clinic visit and/or telephone contact will be scheduled/reconfirmed	Extension of Long-Term Treatment Period from 1 year to 2 years and addition of clinic visits during the extension. Moved the more comprehensive Week 28 visit activities from Section 6.3.2 to Section 6.3.3.

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
	will be scheduled/reconfirmed		
Section 6.3.3 (heading changed)	**Clinic Visit (Week 54 ± 3 days or Early Termination)** *See the Schedule of Events for a detailed summary of activities.* All subjects will stop study drug at the Week 54 visit. Subjects will return to the clinic for the following Week 54/Early Termination (ET) end-of-long term treatment period assessments: ... • Physical examination, vital signs (including orthostatic blood pressure and pulse), and weight • Complete neurological examination ... • *No text* ... *No text*	**Clinic Visits (Weeks 28, 54, and 106 [all ± 3 days] or Early Termination)** *See the Schedule of Events for a detailed summary of activities.* At Weeks 28, 54, and 106 or at the Early Termination Visit, subjects will undergo a more comprehensive evaluation, including: ... • Physical examination (brief physical examination only at Week 28), vital signs (including orthostatic blood pressure and pulse at Weeks 54 and 106/ET), and weight • Complete neurological examination (Weeks 54 and 106/ET only) ... • Re-order study drug (see Operations Manual for further details, Weeks 28 and 54 only) ... Unless a subject discontinues the study early, treatment with study drug will stop at the Week 106 visit.	Addition of clinic visit during extension of Long-Term Treatment Period from 1 year to 2 years. Moved the more comprehensive Week 28 visit activities from Section 6.3.2 to Section 6.3.3.
Section 6.4, Post-Treatment Safety Follow-up	Following discontinuation of study drug at the Week 54 visit, subjects will have a clinic visit at Week 55 for evaluation of safety, dyskinesia and motor function, and a telephone contact at Week 58 for review of AEs and concomitant medication use since Week 55. During the first week after stopping study drug (i.e., through the Week 55 visit), subjects should not take prohibited concomitant medications. Between the Week 55 visit and the Week 58 telephone contact, concomitant medication use is per the discretion of the Investigator.	Following discontinuation of study drug at the Week 106 visit, subjects will have a clinic visit at Week 107 for evaluation of safety, dyskinesia, and motor function and a telephone contact at Week 110 for review of AEs and concomitant medication use since Week 107. During the first week after stopping study drug (i.e., through the Week 107 visit), subjects should not take prohibited concomitant medications. Between the Week 107 visit and the Week 110 telephone contact, concomitant medication use is per the discretion of the Investigator.	Extension of Long-Term Treatment Period from 1 year to 2 years
Section 6.4.1 (heading changed)	**Clinic Visit (Week 55 ± 3 days)** ... All subjects will return one week after the Week 54 or	**Clinic Visit (Week 107 ± 3 days)** ... All subjects will return 1 week after the Week 106 or	Extension of Long-Term Treatment Period from 1 year to 2 years

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
	Early Termination visit...	Early Termination visit...	
Section 6.4.2 (heading changed)	**Telephone Contact (Week 58 ± 3 days)** All subjects will have a follow-up telephone contact at Week 58, 3 weeks after the Week 55 visit (4 weeks after their last dose of study drug [Week 54]), or 3 weeks after the Early Termination visit.	**Telephone Contact (Week 110 ± 3 days)** All subjects will have a follow-up telephone contact at Week 110, 3 weeks after the Week 107 visit (4 weeks after their last dose of study drug [Week 106]), or 4 weeks after the Early Termination visit.	Extension of Long-Term Treatment Period from 1 year to 2 years
Section 6.6.2, Independent Rating of Dyskinesia	To enable a systematic evaluation of the primary endpoint, the AIMS will be digitally video-recorded using a standard protocol at Baseline and at Weeks 6, 15, 28, 41, and 54 (see Appendix 2). The videos from Baseline and Weeks 6, 15, 28, 41, and 54 will be independently reviewed by a blinded central rater(s) who is an expert in movement disorders.	To enable a systematic evaluation of the primary endpoint, the AIMS will be digitally video-recorded using a standard protocol at Baseline and at Weeks 6, 15, 28, 41, 54, and 106 (see Appendix 2). The videos from Baseline and Weeks 6, 15, 28, 41, 54, and 106 will be independently reviewed by a blinded central rater(s) who is an expert in movement disorders.	Extension of Long-Term Treatment Period from 1 year to 2 years
Section 6.7.5, Orthostatic Blood Pressure and Pulse	Orthostatic blood pressure and pulse will be recorded at Week 6 and Week 54/ET.	Orthostatic blood pressure and pulse will be recorded at Weeks 6, 54, and 106/ET.	Extension of Long-Term Treatment Period from 1 year to 2 years
Section 6.7.6, Laboratory Tests	Blood and urine samples will be collected and analyzed, and applicable parameters calculated according to the Standard Operating Procedures (SOPs) at the central laboratory. If abnormal, screening labs may be repeated once to confirm the subject's eligibility.	Blood and urine samples will be collected and tested for the items in Table 3, and applicable parameters will be calculated according to the Standard Operating Procedures (SOPs) at the central laboratory. If abnormal, screening labs may be repeated once to confirm the subject's eligibility. As specified in Table 3, certain lab results obtained in the parent study do not need to be repeated at screening for Study SD-809-C-20. **Table 3: Laboratory Tests**	Indicate that certain labs from parent study do not need to be repeated; clarification
Section 6.7.6, Laboratory Tests	***Labs for Screening Purposes*** • Urine and serum pregnancy tests (women of childbearing potential only) • Follicle Stimulating Hormone for post-menopausal women only. • Hepatitis B surface antigen (HBsAg) ***Other***	***Labs for Screening Purposes*** • Urine pregnancy tests (women of childbearing potential only) ***Lab Results from Parent Study*** • CYP2D6 genotype (blinded) • Prothrombin Time (PT) with International Normalized Ratio (INR)	Specify which labs from parent study do not need to be repeated for Study SD-809-C-20

Section	Amendment 02, dated 08 July 2014	Amendment 03, dated 14 Oct 2015	Reason for Change
	• CYP2D6 genotype (blinded) • Prothrombin Time (PT) with International Normalized Ratio (INR)	• Follicle Stimulating Hormone for post-menopausal women only. • Hepatitis B surface antigen (HBsAg)	
Section 6.7.9, Rating Scales	Subject completed assessments will be available in English, Spanish, and French.	Subject-completed assessments will be available in English, Spanish, Hungarian, German, Polish, Czech, and Slovakian.	Update of translations available for subject-completed assessments
Section 9.5, Clinical Product Complaints (section added)	*Not applicable*	*Section added* *(renumbering of subsequent sections)*	Insertion of standardized language regarding any problems with the physical quality or characteristics of clinical drug supplies
Appendix 1, Site Investigator Signature Page	**I have read and understand Protocol SD-809-C-20 Amendment 02 in its entirety and I agree to all aspects.**	**I have read and understand Protocol SD-809-C-20 Amendment 03 in its entirety and I agree to all aspects.**	Clarification
Appendix 19, Summary of Changes, Amendment 02 (dated 08 July 2014) to Amendment 03 (dated 14 Oct 2015)	*Not applicable*	*Appendix added*	Summarize protocol changes in Amendment 03
Global	*Not applicable*	*Updated dates, section numbers, and tables of contents. Corrected typos; errors in punctuation, grammar, and formatting; and inconsistencies in style.*	

Appendix 20: Protocol Summary of Changes, Amendment 03 (dated 14 Oct 2015) to Amendment 04 (dated 27 Sept 2016)

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
Study Contacts: Sponsor	[redacted]	[redacted]	Administrative changes
Study Contacts: Medical Monitor		[redacted]	
Protocol Synopsis: Study Design	**Titration Period (up to 6 weeks):** As subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo SD-809 dose titration in this study. During titration, the Investigator, in consultation with the subject, will determine when an adequate level of dyskinesia control has been achieved. The dose of SD-809 should be adjusted (upward or downward), in increments of 6 mg per day (up to once per week), until there is adequate control of dyskinesia, the subject experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meets the criteria for a serious adverse event [SAE]),	**Titration Period (up to 6 weeks):** As subjects will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo SD-809 dose titration in this study. During titration, the Investigator, in consultation with the subject, will determine when an adequate level of dyskinesia control has been achieved. The dose of SD-809 should be adjusted (upward or downward), in increments of 6 mg per day (up to once per week), until there is adequate control of dyskinesia, the subject experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meets the criteria for a serious adverse event [SAE]), or the maximal allowable dose is reached. If a subject experiences a clinically significant AE attributable to SD-809,	Clarification of the procedure for dose suspension or withdrawal

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	or the maximal allowable dose is reached. If a subject experiences a clinically significant AE attributable to SD-809, the Investigator will determine if a dose reduction or, suspension, is necessary. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2 to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. ***Although subjects will enter the long-term treatment period after Week 2, titration should continue through Week 6 to optimize dose.***	the Investigator will determine if a dose reduction, dose suspension, or withdrawal from the study is necessary. Prior to withdrawing a subject from the study, the reasons for doing so should be discussed with the Medical Monitor or Sponsor Clinician. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2 to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. ***Although subjects will enter the long-term treatment period after Week 2, titration should continue through Week 6 to optimize dose.***	
Protocol Synopsis: Study Design	**Long-Term Treatment Period (up to 2 years):** During long-term treatment, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a dose level that adequately controls dyskinesia and is well tolerated by the Week 6 visit should have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Interactions with the clinical site for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 106 (i.e., after 2 years of Long-Term Treatment Period). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and only in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's (if appropriate) reports of AEs and dyskinesia control, as well as information from rating scales and safety evaluations, when available. If warranted, study sites are encouraged to conduct periodic phone calls with subjects to ensure adherence	**Long-Term Treatment Period (up to 3 years):** During long-term treatment, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a dose level that adequately controls dyskinesia and is well tolerated by the Week 6 visit should have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Interactions with the clinical site for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 158 (i.e., after 3 years of Long-Term Treatment Period). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and only in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's (if appropriate) reports of AEs and dyskinesia control, as well as information from rating scales and safety evaluations, when available. If warranted, study sites are encouraged to conduct periodic phone calls with subjects to ensure adherence to the treatment regimen and retention of unused drug containers.	Update to clarify Study Design extension

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	to the treatment regimen and retention of unused drug containers.		
Protocol Synopsis, Section: Study Design Post-Treatment Safety Follow-up	Post-Treatment Safety Follow-up: All subjects will discontinue study drug at the Week 106 visit and return for their final clinic visit at Week 107 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout period, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 110, 4 weeks after their last dose of study drug, to evaluate AEs and concomitant medication usage.	Post-Treatment Safety Follow-up: All subjects will discontinue study drug at the Week 158 visit and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout period, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate AEs and concomitant medication usage.	Update to post treatment follow-up schedule
Protocol Synopsis, Dose Regimen	Study drug will be administered as follows: All treatment regimens will be administered twice daily (BID) with meals, approximately 10 hours apart during the day. The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the parent trial. Prior treatment assignment from the parent trial will remain blinded. The maximum total daily dose of SD-809 is 48 mg/day (24 mg BID) unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum total daily dose is 36 mg/day. Daily doses up to 36 mg/day will be given as one tablet BID whereas daily doses of 42 mg/day and 48 mg/day will be given as two tablets BID.	Study drug will be administered as follows: All treatment regimens will be administered twice daily (BID) with meals, approximately 10 hours apart during the day. The starting dose will be SD-809 12 mg/day (6 mg BID) regardless of previous treatment in the parent trial. Prior treatment assignment from the parent trial will remain blinded. The maximum total daily dose of SD-809 is based on body weight: o If body weight <100 kg, the maximum daily dose is 48 mg/day (24 mg BID) unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum total daily dose is 36 mg/day. o If body weight ≥100 kg the maximum daily dose is 60 mg/day (30 mg BID) unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 42 mg/day. Daily doses up to 36 mg/day will be given as one tablet BID whereas daily doses of 42 mg/day, 48 mg/day, 54 mg/day and 60 mg/day will be given as two tablets BID.	Changes in maximum daily dose
Schedule of Events	8 Subjects who have not achieved adequate control of dyskinesia during the study may have up to two blood	Schedule Events (Year 3) Study week: 119, 132, 145, & 158/ET Follow-up: 159 & 162 8 Subjects who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected	Update to Schedule of Events table to extend study for another year

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	samples collected for future pharmacokinetic assessment of α- and β- HTBZ.	within 48 hours of the last dose of study drug for future pharmacokinetic assessment of α- and β- HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor	
3.0 Investigational Plan	This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD for up to 2 years (106 weeks). Approximately 330 subjects who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other SD-809 study for treatment of moderate to severe TD) will be enrolled. The study will be conducted at approximately 80 centers in the U.S., Europe, and possibly other regions. The study is divided into a Screening Period, a Titration Period, a Long-Term Treatment Period, and a Post-Treatment Safety Follow-up Period. For subjects who complete the study, overall study participation will be up to 110 weeks.	This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD for up to 3 years (158 weeks). Approximately 330 subjects who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other SD-809 study for treatment of moderate to severe TD) will be enrolled. The study will be conducted at approximately 80 centers in the U.S., Europe, and possibly other regions. The study is divided into a Screening Period, a Titration Period, a Long-Term Treatment Period, and a Post-Treatment Safety Follow-up Period. For subjects who complete the study, overall study participation will be up to 162 weeks.	
3.1- Investigational Plan	Long-Term Treatment Period (up to 2 years): During the Long-Term Treatment Period, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a stable dose by the Week 6 visit may have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 106 (i.e., after 2 years of Long-Term Treatment Period). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more	Long-Term Treatment Period (up to 3 years): During the Long-Term Treatment Period, subjects will continue titration through Week 6. During titration, all subjects will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Subjects who have not achieved a stable dose by the Week 6 visit may have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 158 (i.e., after 3 years of Long-Term Treatment Period). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's reports of adverse events and	Update to Long-Term Treatment Period from 2 to 3 years

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	often than weekly and in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers.	dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers.	
Protocol 3.1 Investigational Plan	Post-Treatment Safety Follow-up: All subjects will discontinue study drug at the Week 106 visit and return for their final clinic visit at Week 107 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 110, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage. Between the Week 107 visit and the Week 110 telephone contact, concomitant medication use is per the discretion of the Investigator.	Post-Treatment Safety Follow-up: All subjects will discontinue study drug at the Week 158 visit and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage. Between the Week 159 visit and the Week 162 telephone contact, concomitant medication use is per the discretion of the Investigator.	Update to post-treatment safety follow-up
Protocol 3.2 Rationale for Study Design	The present investigation is an open-label safety study of up to 106 weeks of treatment with SD-809 at a pharmacologically active dose and will enroll subjects with drug-induced dyskinesia associated with TD who were previously exposed to either SD-809 or placebo in a parent study.	The present investigation is an open-label safety study of up to 158 weeks of treatment with SD-809 at a pharmacologically active dose (or until SD-809 has a regulatory approval for treatment of TD) and will enroll subjects with drug-induced dyskinesia associated with TD who were previously exposed to either SD-809 or placebo in a parent study.	Clarification of Study Design rationale
Protocol 3.3 Rationale for Dose Selection	*No text*	For subjects with a body weight less than 100 kg, the maximum total daily dose of SD-809 is 48 mg/day (24 mg BID), unless the subject is receiving a strong CYP2D6 inhibitor (e.g., paroxetine; see Appendix 13), in which case the maximum total daily dose is 36 mg/day. For subjects with a body weight of 100 kg, or more, the maximum total daily dose of SD-809 is 60 mg/day (30 mg BID), unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 42 mg/day.	Update for dose selection rationale

<table>
<tr><th>Section</th><th>Amendment 03, dated 14 Oct 2015</th><th>Amendment 04, dated 27 Sept 2016</th><th>Reason for Change</th></tr>
<tr><td>5.2.1 General Guidelines</td><td>• If a subject experiences a clinically significant AE attributable to SD-809, the Investigator will determine if a dose reduction or suspension is necessary.</td><td>• For subjects with body weight less than100 kg, the maximum total daily dose of SD-809 is 48 mg/day (24 mg BID), unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 36 mg/day. For subjects with body weight 100 kg or more, the maximum total daily dose of SD-809 is 60 mg/day (30 mg BID), unless the subject is on a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose is 42 mg/day.

Table 2 Maximum Daily Dose Level During the Maintenance Period
<table>
<tr><td rowspan="2">Body weight (kg)*</td><td colspan="2">Target dose (schedule)</td></tr>
<tr><td>Not CYP2D6 impaired</td><td>On strong CYP2D6 inhibitor</td></tr>
<tr><td><100 kg</td><td>48 mg/day (24 mg BID)</td><td>36 mg/day (18 mg BID)</td></tr>
<tr><td>≥100 kg</td><td>60 mg/day (30 mg BID)</td><td>42 mg/day (21 mg BID)</td></tr>
</table>
• Daily doses up to 36 mg/day will be given as 1 tablet BID, whereas daily doses of 42, 48, 54 and 60 mg/day will be given as 2 tablets BID
• If a subject experiences a clinically significant AE attributable to SD-809, the Investigator will determine if a dose reduction or dose suspension, or withdrawal from the study is necessary. Prior to withdrawing a subject from the study, the reasons for doing so should be discussed with the Medical Monitor or Sponsor Clinician</td><td>Clarification of the treatment regiments</td></tr>
<tr><td>Protocol:
5.2.3 Dose Reduction or Suspension</td><td>5.2.3 Dose Reduction or Suspension
If a subject experiences a clinically significant AE (see Section 7) that is attributed to SD-809, the Investigator will use his or her judgment to determine if a dose reduction, dose suspension or withdrawal from the study is necessary. Prior to withdrawing a subject from</td><td>5.2.3 Dose Reduction or Suspension
If a subject experiences a clinically significant AE (see Section 7) that is attributed to SD-809, the Investigator will use his or her judgment to determine if a dose reduction, dose suspension or withdrawal from the study is necessary. Prior to withdrawing a subject from the study, the reasons for doing so should be</td><td>Clarification of the procedures if a dose reduction, suspension or withdrawal is</td></tr>
</table>

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	the study, the reasons for doing so should be discussed with the Medical Monitor or Sponsor Clinician. Dose adjustments should be made based on all available information including the subject's and caregiver's reports of AEs and dyskinesia control, the clinical assessment of safety and efficacy by the investigator and information from rating scales.	discussed with the Medical Monitor or Sponsor Clinician. Dose adjustments should be made based on all available information including the subject's and caregiver's reports of AEs and dyskinesia control, the clinical assessment of safety and efficacy by the investigator and information from rating scales.	necessary
Protocol: 5.2.3 Dose Reduction or Suspension	Suspensions for more than 7 days must be reviewed by the Medical Monitor. If the subject restarts study drug within 7 days of suspension, the full dose of SD-809 may be resumed without titration. If subject restarts study drug greater than 7 days following a suspension, retitration will be required.	Suspensions for more than 7 days must be reviewed by the Medical Monitor. If the subject restarts study drug within 7 days of suspension, the full dose of SD-809 may be resumed without titration. If subject restarts study drug greater than 7 days following a suspension, re-titration will be required. Dose re-titrations will necessitate additional unscheduled visits and telephone contacts which will be needed to ensure that the subject reaches the appropriate maintenance dose safely and without undue delay, and to ensure adherence to the treatment regimen and retention of any unused drug materials.	Clarifying dose re-titration procedures
Protocol: 6.3 Long Term Treatment Period (up to 3 years)	During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 106 (i.e., after 2 years of Long-Term Treatment Period). Further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg. Dose adjustments should be based on all available information, including the subject's (and caregiver's, if applicable) reports of AEs and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers. At Weeks 28, 54, and 106, subjects will undergo a more comprehensive evaluation, including physical exam, complete neurological exam (Weeks 54 and 106 only), safety labs, 12 lead ECG, urine pregnancy test for women of childbearing potential, and performance of all rating scales.	During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 158 (i.e., after 3 years of Long-Term Treatment Period). Further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg. Dose adjustments should be based on all available information, including the subject's (and caregiver's, if applicable) reports of AEs and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers. At Weeks 28, 54, and 158, subjects will undergo a more comprehensive evaluation, including physical examination, complete neurological exam (Weeks 54 and 158 only), safety labs, 12 lead ECG, urine pregnancy test for women of childbearing potential, and performance of all rating scales.	Update on the long term treatment period

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
Protocol: 6.3.2 Clinic Visits	**Clinic Visits (Weeks 4, 6, 15, 41, 67, 80, and 93 [all ± 3 days])** *See the Schedule of Events for a detailed summary of activities.* Long-Term Treatment Period clinic visits include the following activities: • Assessment of AEs, dyskinesia control (in consultation with the caregiver, if applicable), and concomitant medication use • Weight • Vital signs (at Week 6, include orthostatic blood pressure and pulse) • 12-lead ECG (Weeks 4, 6, and 41) • Clinical laboratory tests: serum chemistry, hematology, and urinalysis (Week 6 only) • AIMS • Video recording of AIMS (Weeks 6, 15, and 41) • UPDRS Part III (motor examination) • BARS • HADS • C-SSRS: Since Last Visit version • ESS • CGIC • PGIC • MoCA© (Weeks 6, 15, 41, 67, 80, 93) • Modified CDQ-24 (Weeks 6, 15, 41) • Assessment of study drug accountability/compliance • Evaluation of study drug dose level and adjustment, if necessary (through Week 6) • Re-order study drug (see Operations Manual for further details) • Next clinic visit and/or telephone contact will be scheduled/reconfirmed Subjects should continue to receive their long-term treatment dose after the Week 6 clinic visit, although further dose adjustments are permitted if clinically	**Clinic Visits (Weeks 4, 6, 15, 41, 67, 80, 93, 119, 132, and 145 [all ± 3 days])** *See the Schedule of Events for a detailed summary of activities.* Long-Term Treatment Period clinic visits include the following activities: • Assessment of AEs, dyskinesia control (in consultation with the caregiver, if applicable), and concomitant medication use • Weight • Vital signs (at Week 6, include orthostatic blood pressure and pulse) • 12-lead ECG (Weeks 4, 6, and 41) • Clinical laboratory tests: serum chemistry, hematology, and urinalysis (Week 6 only) • AIMS • Video recording of AIMS (Weeks 6, 15, and 41) • UPDRS Part III (motor examination) • BARS • HADS • C-SSRS: Since Last Visit version • ESS (excluding at weeks 119 & 145) • CGIC • PGIC • MoCA© (Weeks 6, 15, 41, 67, 80, 93 & 132) • Modified CDQ-24 (Weeks 6, 15, 41) • Assessment of study drug accountability/compliance • Evaluation of study drug dose level and adjustment, if necessary (through Week 6) • Re-order study drug (see Operations Manual for further details) • Next clinic visit and/or telephone contact will be scheduled/reconfirmed Subjects should continue to receive their long-term treatment dose after the Week 6 clinic visit, although further dose adjustments are permitted if clinically indicated.	Update to clinic visits schedule

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	indicated.		
Protocol: 6.3.3 Clinic Visits or Early Termination	6.3.3 Clinic Visits (Weeks 28, 54, and 106 [all ± 3 days] or Early Termination) *See the Schedule of Events for a detailed summary of activities.* At Weeks 28, 54, and 106, or at the Early Termination Visit, subjects will undergo a more comprehensive evaluation, including: Assessment of AEs, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use Physical examination (brief physical exam only at Week 28), vital signs (including orthostatic blood pressure and pulse at Weeks 54, 106/ET, and weight Complete neurological examination (Weeks 54, 106/ET only) Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (women of childbearing potential only) 12-lead ECG AIMS Video recording of AIMS UPDRS Part III (motor examination) BARS HADS C-SSRS: Since Last Visit version ESS CGIC PGIC MoCA© Modified CDQ-24 Assessment of study drug accountability/compliance and collection of all study drug Re-order study drug (see Operations Manual for further details, Weeks 28 and 54 only) The next clinic visit will be scheduled/reconfirmed Unless a subject discontinues the study early, treatment with study drug will stop at the Week 106	6.3.3 Clinic Visits (Weeks 28, 54, 106 and 158 [all ± 3 days] or Early Termination) *See the Schedule of Events for a detailed summary of activities.* At Weeks 28, 54, 106 and 158, or at the Early Termination Visit, subjects will undergo a more comprehensive evaluation, including: Assessment of AEs, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use Physical examination (brief physical examination only at Week 28), vital signs (including orthostatic blood pressure and pulse at Weeks 54, 106, 158/ET), and weight Complete neurological examination (Weeks 54, 106, and 158/ET only) Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (women of childbearing potential only) 12-lead ECG AIMS Video recording of AIMS UPDRS Part III (motor examination) BARS HADS C-SSRS: Since Last Visit version ESS CGIC PGIC MoCA© Modified CDQ-24 Assessment of study drug accountability/compliance and collection of all study drug Re-order study drug (see Operations Manual for further details, Weeks 28 and 54 only) The next clinic visit will be scheduled/reconfirmed Unless a subject discontinues the study early, treatment with study drug will stop at the Week 158 visit. Note: If the subject discontinues from the study early, every	Update to the Clinic visits or early termination

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	visit. Note: If the subject discontinues from the study early, every effort should be made to complete the early termination procedures as outlined above and in the Schedule of Events. In addition, subjects discontinuing prematurely from the study should have a follow-up visit 1 week after discontinuing therapy and a follow-up telephone contact 4 weeks after discontinuing therapy, if possible. The procedures outlined in Section 6.4 should be followed.	effort should be made to complete the early termination procedures as outlined above and in the Schedule of Events. In addition, subjects discontinuing prematurely from the study should have a follow-up visit 1 week after discontinuing therapy and a follow-up telephone contact 4 weeks after discontinuing therapy, if possible. The procedures outlined in Section 6.4 should be followed.	
Protocol: 6.4 Post-Treatment Safety Follow-up	6.4 Post-Treatment Safety Follow-up Following discontinuation of study drug at the Week 106 visit, subjects will have a clinic visit at Week 107 for evaluation of safety, dyskinesia, and motor function and a telephone contact at Week 110 for review of AEs and concomitant medication use since Week 107. During the first week after stopping study drug (i.e., through the Week 107 visit), subjects should not take prohibited concomitant medications. Between the Week 107 visit and the Week 110 telephone contact, concomitant medication use is per the discretion of the Investigator.	6.4 Post-Treatment Safety Follow-up Following discontinuation of study drug at the Week 158 visit, subjects will have a clinic visit at Week 159 for evaluation of safety, dyskinesia, and motor function and a telephone contact at Week 162 for review of AEs and concomitant medication use since Week 159. During the first week after stopping study drug (i.e., through the Week 159 visit), subjects should not take prohibited concomitant medications. Between the Week 159 visit and the Week 162 telephone contact, concomitant medication use is per the discretion of the Investigator.	Update to the post treatment follow-up visit schedule
Protocol: 6.4.1 Clinical Visit 6.4.2 Telephone Contact	6.4.1 Clinical Visit (Week 107 ± 3 days) *See the Schedule of Events for a detailed summary of activities.* All subjects will return 1 week after the Week 106 or Early Termination visit for evaluation of safety, dyskinesia, and motor function. The following activities should be performed: Assessment of AEs, dyskinesia control (in consultation with the caregiver, if appropriate), and concomitant medication use Vital signs Weight AIMS UPDRS Part III (motor examination) BARS HADS	6.4.1 Clinical Visit (Week 159 ± 3 days) *See the Schedule of Events for a detailed summary of activities.* All subjects will return 1 week after the Week 158 or Early Termination visit for evaluation of safety, dyskinesia, and motor function. The following activities should be performed: Assessment of AEs, dyskinesia control (in consultation with the caregiver, if appropriate), and concomitant medication use Vital signs Weight AIMS UPDRS Part III (motor examination) BARS HADS C-SSRS Since Last Visit version ESS Next telephone contact will be scheduled/reconfirmed	Update visit weeks for clinical and telephone

Section	Amendment 03, dated 14 Oct 2015	Amendment 04, dated 27 Sept 2016	Reason for Change
	C-SSRS Since Last Visit version ESS Next telephone contact will be scheduled/reconfirmed 6.4.2 Telephone Contact (Week 110 ± 3 days) All subjects will have a follow-up telephone contact at Week 110, 3 weeks after the Week 107 visit (4 weeks after their last dose of study drug [Week 106]), or 4 weeks after the Early Termination visit. During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about AEs and concomitant medication use since the subject's last evaluation.	6.4.2 Telephone Contact (Week 162 ± 3 days) All subjects will have a follow-up telephone contact at Week 162, 3 weeks after the Week 159 visit (4 weeks after their last dose of study drug [Week 158]), or 4 weeks after the Early Termination visit. During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about AEs and concomitant medication use since the subject's last evaluation.	
Protocol: 6.8 Pharmacokinetic Evaluations	*No text*	6.8 Pharmacokinetic Evaluations Subjects who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected for future pharmacokinetic assessment of α- and β- HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor. The date and time of the last dose of study drug should be recorded along with the date and time of the sample collection.	Clarify pharmacokinetic procedures
Appendix 13: Strong CYP2D6 Inhibitor	After the Screening visit, addition of the above strong CYP2D6 inhibitors is prohibited. Subject's receiving any of the above strong CYP2D6 inhibitors will have a maximal dose of SD-809 of 36 mg per day.	The maximum total daily dose of SD-809 for subjects with body weight less than 100 kg receiving any of the above strong CYP2D6 inhibitors is 36 mg per day. For subjects with body weight of 100 kg or more, receiving any of the above strong CYP2D6 inhibitors, the maximum total daily dose of SD-809 is 42 mg per day.	Update Appendix 13
Appendix 20, Summary of Changes, Amendment 03 (dated 14 Oct 2015) to Amendment 04 (dated 27 Sept 2016)	Not applicable	Appendix added	Summarize protocol changes in Amendment 04
Global	Not applicable	Updated amendment number, dates, section numbers, and tables of contents. Corrected typos; errors in punctuation, grammar, and formatting; and inconsistencies in style.	

Appendix 21: Protocol Summary of Changes, Amendment 04 (dated 27 Sept 2016) to Amendment 05 (dated 08 Feb 2017)

Section	Amendment 04 (dated 27 Sept 2016)	Amendment 05, dated 08 Feb 2017	Reason for Change
Study Contacts: Sponsor Medical Monitor (US) (EU)	[redacted] Not applicable.	[redacted]	Update to contacts and/or telephone numbers. Addition of EU Medical Monitor and back-up
Schedule of Events	Not applicable	Addition of footnote #9 to the "12-lead ECG" activity row, under the unscheduled visits assessment column 9 Subjects undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring (see Section 6.5.1).	To direct the reader to Section 6.5.1, which details the additional ECG monitoring per the protocol.
Protocol Approval Page	[redacted] Principal Investigator for the Study Date	[redacted] Date Date	Removal of the signature for multiple PIs/coordinating investigators. [redacted] is no longer required to sign off.

Section	Amendment 04 (dated 27 Sept 2016)	Amendment 05, dated 08 Feb 2017	Reason for Change
5.2.3 Dose Reduction, Suspension, or Discontinuation	5.2.3 Dose Reduction or Suspension	5.2.3 Dose Reduction, Suspension, or Discontinuation	
	Dose reductions should generally occur in increments of 6 mg/day, except in the case of addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, bupropion), in which case a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. A dose reduction of 6 mg/day can be made by requesting that the next lowest dose level be shipped directly to the subject.	**Dose Reduction** Dose reduction should generally occur in increments of 6 mg/day, except in the case of addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, bupropion), in which case a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. A dose reduction of 6 mg/day can be made by requesting that the next lowest dose level be assigned through the Interactive Response Technology system.	Clarify that a dose reduction is operationalized through the Interactive Response Technology system
	Suspension of study drug for up to 1 week, if warranted, is allowed. **Suspensions of study drug for AEs must be reviewed with the Medical Monitor before therapy is restarted. If study drug is restarted after a suspension for an AE, a dose reduction of 6 mg or more is permitted**. **Suspensions for more than 7 days must be reviewed by the Medical Monitor**. If the subject restarts study drug within 7 days of suspension, the full dose of SD-809 may be resumed without titration. If subject restarts study drug greater than 7 days following a suspension, retitration will be required. Dose re-titrations will necessitate additional unscheduled visits and telephone contacts which will be needed to ensure that the subject reaches the appropriate maintenance dose safely and without undue delay, and to ensure adherence to the treatment regimen and retention of any unused drug materials.	**Suspension** Suspension of study drug for up to 1 week, if warranted, is allowed. **Suspensions of study drug for AEs must be reviewed with the Medical Monitor before therapy is restarted**. If study drug is restarted after a suspension for an AE, a dose reduction of 6 mg or more is permitted. If a subject's serum potassium or magnesium falls below the lower limit of normal, study drug must be suspended. The Medical Monitor must be contacted to determine the appropriate investigation and treatment. SD-809 may only be restarted once serum potassium or magnesium have normalized. Suspensions for more than 7 days must be reviewed by the Medical Monitor. If the subject restarts study drug within 7 days of suspension, the full dose of SD-809 may be resumed without titration. If subject restarts study drug greater than 7 days following a suspension, re-titration will be required. Dose re-titrations will necessitate additional	As hypokalemia and hypomagnesiam may contribute to QT prolongation, criteria for suspending treatment have been added in case a subject's potassium or magnesium levels fall below the lower limit of normal.

Section	Amendment 04 (dated 27 Sept 2016)	Amendment 05, dated 08 Feb 2017	Reason for Change
	The reason for a dose reduction or suspension must be clearly documented.	unscheduled visits and telephone contacts which will be needed to ensure that the subject reaches the appropriate maintenance dose safely and without undue delay, and to ensure adherence to the treatment regimen and retention of any unused drug materials. **Discontinuation** Discontinue study drug and complete an early termination visit if, based on readings of 12-lead ECGs interpreted in the central ECG laboratory, the subject meets either of the following criteria: • a mean[f] QTcF value >500 msec or • a mean[f] change in QTcF of >60 msec from Baseline **The reason for a dose reduction, suspension, or discontinuation must be clearly documented**.	Addition of subject discontinuation criteria regarding clinically significant QTc observations.
6.5.1 Unscheduled Visit(s) for Change in Antipsychotic Regimen	Not applicable	6.5.1 Unscheduled Visit(s) for Change in Antipsychotic Regimen Subjects undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring. In such cases, the Investigator should contact the Medical Monitor to review these procedures. • Subjects undergoing such a change in **oral** antipsychotic treatment should have an unscheduled visit between 1-2 weeks thereafter. • Subjects undergoing an increase in dose of a **long-acting injectable** (LAI) antipsychotic, switching to LAI treatment, or having an additional LAI antipsychotic	Given the potential for many antipsychotics to prolong the QT interval, additional ECG monitoring will be added if a patient increases antipsychotic dose, switches to a new antipsychotic, or has a new antipsychotic treatment added to their regimen.

Section	Amendment 04 (dated 27 Sept 2016)	Amendment 05, dated 08 Feb 2017	Reason for Change
		treatment added to their regimen should have an unscheduled visit within the following timeframe, based on the prescribed LAI antipsychotic: o 4-5 weeks: fluphenazine decanoate o 8-9 weeks: risperidone LA, haloperidol decanoate, olanzapine pamoate, Zuclopenthixol decanoate o 12-13 weeks: all other LAI antipsychotics On the morning of the clinic visit, the subject should hold their SD-809 dose until they are in the clinic. Upon reaching clinic, the following activities should be performed: • Administer the morning dose of SD-809 with a meal or light snack • Collect a 12-lead ECG 3 hours after SD-809 administration following at least 5 minutes of rest in a supine or semi-recumbent position. o Based on the ECG machine reading, if QTcF value is >500 msec or there is a change from Baseline in QTcF value of >60 msec, two additional 12-lead ECGs should be collected as soon as practical. There should be at least 5 minutes between ECGs. • Transmit ECGs to the central laboratory on the same day that they are collected.	
6.5.2 Unscheduled Telephone Visit(s)	Not applicable	6.5.2 Unscheduled Telephone Visits	Addition of section head to enhance protocol structure
6.7.7 12-Lead Electrocardiogram	All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.	All ECGs will be performed after at least 5 minutes rest in a supine or semi-recumbent position.	Update to ECG position terminology
6.9.1 Concomitant Medications	**Allowed Concomitant Medications** Subjects receiving psychoactive medications (including, but not limited to, neuroleptics [see Appendix 16], benzodiazepines,	**Allowed Concomitant Medications** <u>Stable dosing</u> Subjects receiving psychoactive medications (including, but not limited to, neuroleptics	Increased breakdown of allowed concomitant medications. Addition of “antipsychotics” subsection to clarify the

Section	Amendment 04 (dated 27 Sept 2016)	Amendment 05, dated 08 Feb 2017	Reason for Change
	anticonvulsants, and mood stabilizers) must be on a stable dose for ≥30 days (oral medication) before Screening and in the opinion of the treating psychiatrist, no changes in drug or dose are expected in the next 3 months. After 3 months, changes in psychoactive medications are allowed if approved by the Investigator. Any changes in concomitant medications must be documented in the eCRF. Subjects receiving antidepressant therapy must be on a stable dose for 45 days before Screening. Subjects receiving long acting (depot) medications must have been on stable therapy (dose, frequency) for ≥3 months before Screening. Female subjects on hormonal contraception (approved oral, transdermal, or depot regimen) for birth control must be on a stable dose for at least 3 months prior to Screening and through study completion. Subjects will be instructed to inform the study Investigator of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF.	[see Appendix 16], benzodiazepines, anticonvulsants, and mood stabilizers) must be on a stable dose for ≥30 days (oral medication) before Screening and in the opinion of the treating psychiatrist, no changes in drug or dose are expected in the next 3 months. After 3 months, changes in psychoactive medications are allowed if approved by the Investigator. Any changes in concomitant medications must be documented in the eCRF. <u>Antipsychotics</u> Considering the potential of antipsychotic drugs to prolong the QT interval, additional ECG monitoring is required if the Investigator 1) increases the dose of a patient's current antipsychotic treatment, 2) switches the patient to a different antipsychotic treatment, or 3) adds a new antipsychotic treatment to the patient's regimen. In such cases, subjects should have an unscheduled visit within 1-2 weeks for a change in oral antipsychotic treatment, or have an unscheduled visit within 4-5 weeks, 8-9 weeks, or 12-13 weeks (depending upon the prescribed LAI) for a change in their LAI antipsychotic treatment, to have a repeat 12-lead ECG following their usual SD-809 dose (see Section 6.5.1). <u>Antidepressants</u> Subjects receiving antidepressant therapy must be on a stable dose for 45 days before Screening. Subjects receiving long acting (depot) medications must have been on stable therapy (dose, frequency) for ≥3 months before Screening. <u>Other</u> Female subjects on hormonal contraception (approved oral, transdermal, or depot	additional ECG monitoring that will take place due to the potential for antipsychotic drugs to prolong the QT interval

Section	Amendment 04 (dated 27 Sept 2016)	Amendment 05, dated 08 Feb 2017	Reason for Change
		regimen) for birth control must be on a stable dose for at least 3 months prior to Screening and through study completion. Subjects will be instructed to inform the study Investigator of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF.	
6.11 Withdrawal Criteria	• Intolerable/unacceptable adverse events;	• Intolerable/unacceptable adverse events (see Section 5.2.3 for QTcF discontinuation criteria);	Addition of cross-reference to newly inserted rules on QTcF discontinuation criteria
Appendices 7 - 12	Appendices 7 - 12 were in advertently left out of Amendment 04	Appendices 7 - 12 have now been inserted back into the protocol	Fix/update
Appendix 14 Prohibited or Restricted QT Prolonging Drugs	Not applicable	Addition of the drug, Thioridazine, to Appendix 14	Thioridazine is categorized as a prohibited QT prolonging drug
Appendix 15 Dopamine Receptor Antagonists	Thioridazine “Typical Dosing” column: Initial: 50-100 mg 3 times/day; up to 800 mg/day	Thioridazine “Typical Dosing” column: Prohibited	Update to the drug, Thioridazine, in the list of Dopamine Receptor Antagonists. Dosing with Thioridazine is now prohibited
Appendix 21, Summary of Changes, Amendment 04 (dated 27 Sept 2016) to Amendment 05 (dated 08 Feb 2017)	Not applicable	Appendix added	Summarize protocol changes in Amendment 05
Global	Not applicable	Updated amendment number, dates, section numbers, and tables of contents. Corrected typos; errors in punctuation, grammar, and formatting; and inconsistencies in style.	

TEVA Pharmaceuticals

LETTER OF CLARIFICATION 01

Study number: SD-809-C-20

Clinical Study Protocol Amendment 4.0

An Open-Label, Long-Term Safety Study of Sd-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia

Dated: 27 September 2016

EudraCT number: 2014-001891-73

08 Feb 2017

Dear Investigator and Study Coordinator,

The purpose of this letter of clarification is to notify you of an inadvertent omission of the content for Appendices 7 – 12 inclusive when protocol amendment 4.0 was published. Although the header page for each appendix is present, the specific content was accidently omitted. Should you have a need to refer to the content please reference the previous protocol version Amendment 3.0 for appendices 7 – 12 as these appendices have not changed from the previous protocol.

This omission is **considered nonsubstantial** and will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact me at [redacted] or by email to [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

[redacted]

Global Branded Products, Clinical Operations
Teva Pharmaceuticals

Teva Pharmaceuticals 41 Moores Road PO Box 4011 | Frazer PA 19355 | [redacted]

Appendix 22: Protocol Summary of Changes, Amendment 05 (dated 08 Feb 2017) to Amendment 06 (dated 23 Jan 2018)

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
Study Contacts: Sponsor	Auspex Pharmaceuticals, Inc. 3333 N. Torrey Pines Court, Suite 400 La Jolla, CA 92037 USA Tel: [redacted] Fax [redacted] [redacted] Vice President, Clinical Development, Teva USA Tel: + [redacted] Email: [redacted] [redacted] Sr Mgr, Global Clinical Project Mgmt Global Clinical Operations, CNS & Pain Tel: [redacted] E-mail: [redacted] C-20 Study Phone [redacted]	Auspex Pharmaceuticals, Inc. 41 Moores Road Frazer, Pennsylvania 19355 USA [redacted] Vice President, TA Head, Specialty R&D Tel: [redacted] E-mail: [redacted] [redacted] Sr Mgr, Global Clinical Project Mgmt Global Clinical Operations, CNS & Pain Tel: + [redacted] E-mail: [redacted] Study SD-809-C-20 Phone [redacted]	Updated to Sponsor contacts and/or telephone numbers. Updated C-20 Study Phone to Study SD-809-C-20 Phone
Medical Monitor (US)	[redacted] Tel: [redacted] E-mail: [redacted] [redacted] c E-mail [redacted]	[redacted] E-mail: [redacted] [redacted] E-mail: [redacted]	
Medical Monitor (EU)	[redacted] Email: [redacted] [redacted]	[redacted] Email: [redacted] [redacted]	
Schedule of Events	Not applicable	First table designated as Part A and footnotes updated to reflect optional move to Part B; additional table created for Part B table. Columns	Updated to designate Part A and Part B and create Randomization Withdrawal Period

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		include Part B Pre-withdrawal Visit, Part B Post-withdrawal Visit, EOT/ET visit, Follow-up visit (ET only), Follow-up Call, and Unscheduled.	
Study Schematic Diagram	Not applicable	Study Schematic Diagram (Parts A and B)	Added study schematic diagram for Parts A and B
Protocol Approval Page	[redacted] Vice President, Clinical Development Teva USA Date	[redacted] Vice President, TA Head, Specialty R&D Teva Pharmaceuticals Date	Updated to the sponsor's clinical signatory
List of Abbreviations	Not applicable	Updated	Updated to include abbreviations required in new amendment text
1.4 Introduction SD-809 (Deutetrabenazine)	The safety and pharmacokinetics of oral SD-809 have been evaluated in five Phase 1 studies in healthy adult volunteers. Additionally, two Phase 3 studies in adult patients with chorea associated with HD, and one Phase 1b study in adolescent patients with tics associated with Tourette syndrome are ongoing at this time.	The safety and pharmacokinetics of oral SD-809 have been evaluated in five Phase 1 studies in healthy adult volunteers. Additionally, two Phase 3 studies in adult patients with chorea associated with HD and one Phase 1b study in adolescent patients with tics associated with Tourette syndrome have been completed.	Updated study statuses
Protocol Synopsis, Objectives Section 2 Study Objectives	The objectives of this study are: • Evaluate the safety and tolerability of long-term maintenance therapy with SD-809 • Evaluate the efficacy of long-term maintenance therapy of SD-809 to reduce the severity of abnormal involuntary movements of TD	The objectives of this study are: • Evaluate the safety and tolerability of long-term maintenance therapy with SD-809 • Evaluate the efficacy of long-term maintenance therapy of SD-809 to reduce the severity of abnormal involuntary movements of TD • Evaluate the persistence of the therapeutic effect of SD-809	Added objective for Part B
Section 3 Investigational Plan	This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD for up to 3 years (158 weeks). Approximately 330 subjects who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other SD-809 study for treatment of moderate to severe TD) will be enrolled.	This is an open-label, single-arm study designed to evaluate the long-term safety and tolerability of SD-809 for the treatment of subjects with moderate to severe drug-induced TD. Approximately 330 subjects who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other SD-809 study for treatment of moderate to severe TD) will be enrolled. The study will be conducted at approximately 80 centers in the U.S., Europe, and possibly other regions. The study is divided into 2 parts, Part A and Part B. These parts	Updated study parts to include Randomization Withdrawal Period (Part B)

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
	The study will be conducted at approximately 80 centers in the U.S., Europe, and possibly other regions. The study is divided into a Screening Period, a Titration Period, a Long-Term Treatment Period, and a Post-Treatment Safety Follow-up Period. For subjects who complete the study, overall study participation will be up to 162 weeks.	include a Screening Period (Part A), a Titration Period (Part A), a Long-Term Treatment Period (Part A), a Double-Blind, Randomized Withdrawal Period (Part B), treatment after completion of the Randomized Withdrawal Period (Part B), and a Post-Treatment Safety Follow-up Period (Part A and Part B).	
Section 3.1 Study Design Section 5.2.1 General Guidelines 5.2.4 Dose Reduction, Suspension, or Discontinuation	Prior to withdrawing a subject from the study, the reasons for doing so should be discussed with the Medical Monitor or Sponsor Clinician.	~~Prior to withdrawing a subject from the study, the reasons for doing so should be discussed with the Medical Monitor or Sponsor Clinician.~~	Removed requirement for discussion with Medical Monitor or Sponsor clinician
Protocol Synopsis, Study Design Section 3.1 Study Design	Informed consent/assent will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Subjects who meet the selection criteria will be eligible to participate.	Informed consent/assent (Part A) will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Subjects who meet the selection criteria will be eligible to participate. Informed consent/assent for Part B will be obtained after Amendment 06 implementation and before any study procedures related to Part B are performed.	Updated to include informed consent for Part B
Protocol Synopsis, Study Design Section 3.1 Study Design	Long-Term Treatment Period (up to 3 years) During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 158 (i.e., after 3 years of Long-Term Treatment Period). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary,	Long-Term Treatment Period (Week 3 until the last dose in Part A) During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at the last dose in Part A (completion of Part A=Week 158 or beginning of Part B after Amendment 06 implementation). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in	Changed length of Long-Term Treatment Period to indicate that treatment will end at last dose of Part A) Added dose reduction instructions to include CYP2D Text added to clarify Part A and Part B timing

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
	but not more often than weekly and in increments of 6 mg per day. Dose adjustments should be based on all available information, including the subject's and caregiver's reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers. Not applicable	increments of 6 mg per day. In the case of the addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, and bupropion), a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. Dose adjustments should be based on all available information, including the subject's and caregiver's reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the subjects to ensure adherence to the treatment regimen and retention of unused drug containers. Subjects who have been on a stable dose of SD-809 and any concomitant dopamine receptor antagonist (DRA) for a minimum of 4 weeks will be invited to participate in the Randomized Withdrawal Period (Part B) at the next routine visit at the site after approvals from IRB/Ethics Committee and as required by country regulations. If the subject chooses to participate in Part B, then participation in Part A will end. Subjects who decline to participate in Part B will continue in Part A until Week 158. Subjects who decline participation in Part B will be given an ongoing option to participate at subsequent study visits.	
Protocol Synopsis, Study Design Section 3.1 Study Design	Not applicable	<u>Part B:</u> Part B will consist of a double-blind, randomized withdrawal period; treatment with SD-809; and the post-treatment safety follow-up. The Randomized Withdrawal Period will be 1 week (+3 days maximum) in duration and will consist of 2 visits, the Pre-withdrawal Visit and the Post-withdrawal Visit. After the Randomized Withdrawal Period, the subjects will resume treatment with SD-809 on the prior established dose for an additional 12 weeks until end of treatment (EOT). At the beginning of the Randomized Withdrawal	Added Randomization Withdrawal Period (Part B)

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		Period, subjects will be randomized in a blinded fashion to either SD-809 (current dose) or placebo in a 1:1 ratio stratified by concomitant DRA usage. Up to 194 subjects (active subjects as of the approval date of Amendment 06) will be randomized (SD-809 or placebo). Subjects will be required to sign a written informed consent. Subjects will need to be on a stable dose of SD-809 and any concomitant DRA for a minimum of 4 weeks before starting the Randomized Withdrawal Period. Subjects will be scheduled to return 1 week (+3 days maximum) after the Pre-withdrawal Visit of the Randomized Withdrawal Period for efficacy and safety assessments. At the end of this period, subjects will continue treatment with SD-809 at the previous dose administered before the Randomized Withdrawal Period (last dose in Part A). Treatment with SD-809 will continue for 12 weeks until the EOT visit. Video ratings of the AIMS will occur at the Pre-withdrawal Visit, the Post-withdrawal Visit, and the EOT/ET visit.	
Protocol Synopsis, Study Design Section 3.1 Study Design	**Post-Treatment Safety Follow-up:** All subjects will discontinue study drug at the Week 158 visit and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week washout, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage. Between the Week 159 visit and the Week 162 telephone contact, concomitant	**Post-Treatment Safety Follow-up:** **Part A**: Subjects who do not participate in Part B will continue in Part A, discontinue study drug at the Week 158 visit, and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week follow-up period, subjects should continue to not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage. Subjects who discontinue study drug in Part A will complete an ET visit; a follow-up clinic visit	Updated post-treatment safety follow-up to include Part B

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
	medication use is per the discretion of the Investigator.	1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET. **Part B**: Subjects who complete the Randomized Withdrawal Period and subsequent 12 weeks of treatment will complete an EOT visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT. Subjects who discontinue study drug in Part B will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.	
Section 3.2 Rationale for Study Design	The study is designed to evaluate the long-term safety and tolerability of SD-809 in subjects with moderate to severe dyskinesia associated with TD.	The study is designed to evaluate the long-term safety and tolerability of SD-809 in subjects with moderate to severe dyskinesia associated with TD (Part A) and the persistence or maintenance of the therapeutic effect of SD-809 in subjects with TD (Part B).	Updated to include Randomized Withdrawal Period (Part B)
Section 3.2 Rationale for Study Design	The present investigation is an open-label safety study of up to 158 weeks of treatment with SD-809 at a pharmacologically active dose (or until SD-809 has a Regulatory approval for treatment of TD) and will enroll subjects with drug-induced dyskinesia associated with TD who were previously exposed to either SD-809 or placebo in a parent study.	The present investigation is an open-label safety study with a nested, randomized, double-blind, 1-week withdrawal period of SD-809. The study will enroll subjects with TD who were previously exposed to either SD-809 or placebo in a parent study.	Updated to include Randomized Withdrawal Period (Part B)

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
Section 5.1 Study Drug	5.1 Study Drug During titration/dose adjustment, SD-809 tablets will be labeled according to applicable regulatory guidelines and supplied in weekly blister packs as 6, 9, 12, 15, and/or 18 mg tablets. Each blister pack will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies. **During long-term treatment, SD-809 will be supplied in 30 count bottles and labeled according to applicable regulatory guidelines.**	5.1 Study Drug 5.1.1 SD-809 During titration/dose adjustment, SD-809 tablets will be labeled according to applicable regulatory guidelines and supplied in weekly blister packs as 6, 9, 12, 15, and/or 18 mg tablets. Each blister pack will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies. **During long-term treatment, SD-809 will be supplied in 30-count bottles and labeled according to applicable regulatory guidelines.** During the 1-week Randomized Withdrawal Period, SD-809 will be supplied in 20-count bottles and labeled according to the applicable regulatory guidelines. 5.1.2 Placebo (Part B: Double-Blind, Randomized Withdrawal Period Only) Placebo tablets are identical in appearance to the SD-809 and contain the same inactive ingredients as SD-809.	Updated to include Randomized Withdrawal Period Added Section 5.1.2 to include placebo used in the Randomized Withdrawal Period
Section 5.2.2 Dosing in Long-Term Treatment (Week 3 Until the Last Dose in Part A)	5.2.2 Dosing in Long-Term Treatment (Weeks 3 to 158)	5.2.2 Dosing in Long-Term Treatment (Week 3 Until the Last Dose in Part A)	Updated to extend treatment to last dose in Part A
Protocol Synopsis, Dose Regimen Section 5.2.3 Dosing in the Double-Blind, Randomized Withdrawal Period	Not applicable	5.2.3 Dosing in the Double-Blind, Randomized Withdrawal Period Subjects in the Randomized Withdrawal Period will continue to receive their current dose of SD-809 or will receive matching placebo. At the end of the Randomized Withdrawal Period, subjects will continue with, or return to, the same dose of SD-809 taken before the Randomized Withdrawal Period (last dose in Part A), beginning the day after the Post-withdrawal Visit and	Added section 5.2.3 to include dosing information for the Randomized Withdrawal Period Added Table 3: Titration Schedule After 1-Week Randomized Withdrawal Period (if Necessary)

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		continuing for 12 weeks. Subjects who do not return for the Post-withdrawal Visit within the 10 days (1 week [+3 days maximum]) may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary) per the guidelines in Table 3. Titration is not permitted during the Randomized Withdrawal Period and will be allowed after return to open-label dosing.	
Section 5.2.4 Dose Reduction, Suspension, or Discontinuation	***Discontinuation*** Discontinue study drug and complete an early termination visit if, based on readings of 12-lead ECGs interpreted in the central ECG laboratory, the subject meets either of the following criteria: • a mean QTcF value >500 msec or • a mean change in QTcF of >60 msec from Baseline **The reason for a dose reduction, suspension, or discontinuation must be clearly documented.**	***Discontinuation*** Discontinue study drug and complete an ET visit if, based on Investigator evaluation of readings of 12-lead ECGs, the subject meets either of the following criteria: • a mean QTcF value >500 msec or • a mean change in QTcF of >60 msec from Baseline **The reason for a dose reduction, suspension, or discontinuation must be clearly documented.**	Updated Discontinuation to indicate that Investigator should evaluate ECG readings
Section 5.4 Accountability of Study Drug	Not applicable	Prior to the Pre-withdrawal Visit and Post-withdrawal Visit, the Investigator or designated site staff must place a call to the subject as a reminder to bring all remaining study drugs to the visit. The Investigator or designated site staff must collect the study drug(s) from the subject and conduct drug accountability.	Added reminder call and instruction to collect all study drug before subject can start blinded treatment in Part B
Section 6.2 Dose Adjustment/Titration Period	**Once adequate control of dyskinesia has been achieved or the maximum allowable dose has been reached, the dose of SD-809 should not be increased further.**	**Once adequate control of dyskinesia has been achieved, the dose of SD-809 should not be increased further.**	Updated to align with Sections 3.2 and 5.2.1

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
Section 6.3 Long-Term Treatment Period (Week 3 Until the Last Dose in Part A)	Long-Term Treatment Period (Up to 3 Years) During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 158 (i.e., after 3 years of Long-Term Treatment Period). Further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg.	Long-Term Treatment Period (Week 3 Until Last Dose in Part A) During the remainder of the Long-Term Treatment Period, subjects will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at the last dose in Part A (completion of Part A=Week 158 or beginning of Part B after Amendment 06 implementation). Further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg.	Updated to extend treatment to last dose in Part A
Section 6.3.3 Clinic Visits (Part A) (Weeks 28, 54, 106 and 158 [All ± 3 Days] or Early Termination)	Unless a subject discontinues the study early, treatment with study drug will stop at the Week 158 visit.	Unless a subject discontinues the study early or opts to participate in Part B, treatment with study drug will stop at the Week 158 visit.	Updated to include the subject option to participate in Part B
Section 6.4 Double-Blind, Randomized Withdrawal Period (Part B)	Not applicable	6.4 Double-Blind, Randomized Withdrawal Period (Part B) *See the Schedule of Events for a detailed summary of activities.* At the Pre-withdrawal Visit and Post-withdrawal Visit (1 week [+3 days maximum] from the Pre-withdrawal Visit), the following activities should be performed: • Obtain or verify informed consent or assent (for subjects who do not have a legally authorized representative) after Amendment 06 implementation (Pre-withdrawal Visit only). • Randomize subject via IRT and dispense study drug (Pre-withdrawal Visit only) • Assessment of adverse events, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use • Vital signs (Pre-withdrawal Visit to include orthostatic blood pressure and pulse) and weight	Added Section 6.4 Double-Blind, Randomized Withdrawal Period

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		• Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (Pre-withdrawal Visit only; women of childbearing potential only) • Single pharmacokinetic (PK) blood sample (Post-withdrawal Visit only) • 12-lead ECG • AIMS • Video recording of AIMS • UPDRS Part III (motor examination) • BARS • HADS • C-SSRS: Since Last Visit version • ESS • MoCA© • Assessment of study drug accountability/compliance and collection of all study drug before randomization into the Randomized Withdrawal Period and at the end of the Randomization Withdrawal Period • Subjects will be provided with a sufficient supply of study drug (blinded at Pre-withdrawal Visit). • The next clinic visit will be scheduled/reconfirmed. 6.4.1 Clinic Visits (Part B Open-label Treatment) End of Treatment or Early Termination *See the Schedule of Events for a detailed summary of activities.* At the Part B EOT or Part B ET visit, subjects will undergo a more comprehensive evaluation, including: • Assessment of adverse events, dyskinesia control (in consultation with the subject and caregiver, if applicable), and concomitant medication use	

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		• Physical examination, vital signs (including orthostatic blood pressure and pulse), and weight • Complete neurological examination • Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (women of childbearing potential only) • 12-lead ECG • AIMS • Video recording of AIMS • UPDRS Part III (motor examination) • BARS • HADS • C-SSRS: Since Last Visit version • ESS • MoCA© • Assessment of study drug accountability/compliance and collection of all study drug • The next clinic visit will be scheduled/reconfirmed Unless a subject discontinues the study early, treatment with study drug will stop at the EOT visit. **Note:** If the subject discontinues from the study early, every effort should be made to complete the ET procedures as outlined above and in the Schedule of Events. In addition, subjects discontinuing prematurely from the study should have a follow-up visit 1 week after discontinuing therapy and a follow-up telephone contact 4 weeks after discontinuing therapy, if possible. The procedures outlined in Section 6.4 should be followed.	
Section 6.5 Post-Treatment Safety Follow-Up	Following discontinuation of study drug at the Week 158 visit, subjects will have a clinic visit at Week 159 for evaluation of safety, dyskinesia, and motor	Following discontinuation of study drug at the Week 158 visit in Part A, subjects will have a clinic visit at Week 159 for evaluation of safety, dyskinesia, and motor function and a telephone	Updated visit designations

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
	function and a telephone contact at Week 162 for review of AEs and concomitant medication use since Week 159. During the first week after stopping study drug (i.e., through the Week 159 visit), subjects should not take prohibited concomitant medications. Between the Week 159 visit and the Week 162 telephone contact, concomitant medication use is per the discretion of the Investigator.	contact at Week 162 for review of adverse events and concomitant medication use since Week 159. Following discontinuation of study drug at the ET visit in Part A, subjects will have a clinic visit 1 week later for evaluation of safety, dyskinesia, and motor function and a telephone contact 4 weeks after the last dose for review of adverse events and concomitant medication use since ET. Following discontinuation of study drug at the EOT visit in Part B, subjects will have a telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT. Following discontinuation of study drug at the ET visit in Part B, subjects will have a clinic visit 1 week later for evaluation of safety, dyskinesia, and motor function and a telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET. During the first week after stopping study drug, subjects should not take prohibited concomitant medications. Between the Week 158, EOT, or ET visit and the follow-up telephone contact, concomitant medication use is per the discretion of the Investigator.	
Section 6.5.1 Clinic Visit (1 Week after Early Termination ±3 Days)	6.4.1 Clinic Visit (Week 159 ± 3 Days) All subjects will return 1 week after the Week 158 or Early Termination visit for evaluation of safety, dyskinesia, and motor function. The following activities should be performed:	6.5.1 Clinic Visit (Week 159 or 1 Week after Early Termination ±3 Days) All subjects will return 1 week after Week 158 (Part A) or the ET visit (Part A or Part B) for evaluation of safety, dyskinesia, and motor function. The following activities should be performed:	Updated final clinic visit description from to include text for subjects who terminated early in Part A or Part B

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
Section 6.5.2 Telephone Contact (4 Weeks After EOT/ET ± 3 Days)	6.4.2 Telephone Contact (Week 162 ± 3 Days) All subjects will have a follow-up telephone contact at Week 162, 3 weeks after the Week 159 visit (4 weeks after their last dose of study drug [Week 158]), or 4 weeks after the Early Termination visit. During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about AEs and concomitant medication use since the subject's last evaluation.	6.5.2 Telephone Contact (Week 162 ± 3 Days or 4 Weeks After EOT/ET ± 3 Days) All subjects will have a follow-up telephone contact at Week 162 (4 weeks after their last dose of study drug [Week 158]) (Part A); or 4 weeks after the EOT visit (Part B); or 4 weeks after the ET visit (Part A or Part B). During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about adverse events and concomitant medication use since the subject's last evaluation.	Updated time period to 4 weeks after EOT/ET visit
Section 6.8.5 Orthostatic Blood Pressure and Pulse	Orthostatic blood pressure and pulse will be recorded at Weeks 6, 54, 106, and 158/ET.	Orthostatic blood pressure and pulse will be recorded at Weeks 6, 54, 106, 158/ET, the Pre-withdrawal Visit, and EOT.	Added Pre-withdrawal Visit and EOT
Section 6.10.1 Concomitant Medications	Not applicable	Valbenazine	Added valbenazine to the Prohibited Concomitant Medications list
Section 8.1 Analysis Populations	Intent-to-Treat (ITT) Population: The ITT Population will include all enrolled subjects in the study. All efficacy measures will be summarized using the ITT Population.	Intent-to-Treat (ITT) Population: The ITT Population will include all enrolled subjects in the study. All efficacy measures in Part A will be summarized using the ITT Population. Randomized Withdrawal ITT Population: The Randomized Withdrawal ITT Population will include all subjects enrolled to Part B of the study. Randomized Withdrawal Modified ITT (mITT) Population: The Randomized Withdrawal mITT Population will include all subjects enrolled in Part B who receive study drug during the Randomized Withdrawal Period and have a centrally read AIMS score at both the Pre-withdrawal Visit and the Post-withdrawal Visit. All efficacy measures in the Randomized Withdrawal Period will be analyzed using the Randomized Withdrawal mITT population.	Updated to include Randomized Withdrawal populations
Synopsis, Safety Endpoints Section 8.4 Safety	The following safety endpoints will be assessed: • Incidence of AEs, SAEs, severe	The following safety endpoints will be assessed: • Incidence of adverse events, serious adverse events, severe adverse events, drug-related	Added Randomized Withdrawal Period endpoints >30 ms added to Part A change

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
Endpoints	AEs, drug-related AEs, AEs leading to withdrawal during the following periods: o Overall o During titration o During long-term treatment • Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes from baseline in vital signs • Observed values in ECG parameters and abnormal findings • Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms • Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA© • Duration of time to achieve stable doing of SD-809	adverse events, adverse events leading to withdrawal during the following periods: o Overall o During titration o During long-term treatment • Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes from baseline in vital signs • Observed values in ECG parameters and abnormal findings • Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms • Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA© • Duration of time to achieve stable dosing of SD-809 The following secondary safety endpoints will be assessed in Part B Double-Blind, Randomized Withdrawal Period • Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, and adverse events leading to withdrawal • Observed values and changes from start of randomized withdrawal in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes from start of randomized withdrawal in vital signs • Observed values in ECG parameters and abnormal findings • Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a	from baseline endpoint as standard QTcF safety endpoint

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		change from Baseline in QTcF of >30 ms or >60 ms • Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA©	
Protocol Synopsis, Efficacy Measures Section 8.5 Efficacy Measures	The following efficacy measures will be assessed during Part A: • The change in AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by blinded central video rating. • The change in AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by the site rating. • The proportion of subjects who are a treatment success based on the CGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study. • The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline of this study at each visit that this is measured. • The change in the modified CDQ-24 score from Baseline of this study at each visit that this is measured. • The proportion of subjects who are a treatment success based on the PGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study.	The following efficacy measures will be assessed during Part A: • The change in AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by the site rating. • The proportion of subjects who are a treatment success based on the CGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study. • The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline of this study at each visit that this is measured. • The change in the modified CDQ-24 score from Baseline of this study at each visit that this is measured. • The proportion of subjects who are a treatment success based on the PGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study. • The percent change in AIMS score from Baseline of this study at each visit that this is measured.	Deleted AIMS video recording measure

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
	• The percent change in AIMS score from Baseline of this study at each visit that this is measured. • Based on the change in AIMS score from Baseline of this study at each visit that this is measured, as assessed by blinded central video rating, the cumulative proportion of responders ranging from a 10% improvement from Baseline to a 90% improvement from Baseline in steps of 10 percentage points.		
Protocol Synopsis, Efficacy Measures Section 8.5 Efficacy Measures	Not applicable	The following efficacy measures will be assessed during Part B (Randomized Withdrawal Period): • Primary efficacy endpoint: change from Pre-withdrawal Visit AIMS scores (items 1 through 7) as assessed by blinded central video rating to the Post-withdrawal Visit between subjects treated with SD-809 and subjects treated with placebo.	Updated to include Randomized Withdrawal Period primary and secondary endpoints
Protocol, Statistics Section 8.6 Efficacy Analysis (Randomized Withdrawal Period; Part B)	Not applicable	8.6 Efficacy Analysis (Randomized Withdrawal Period; Part B) Analysis of the change in centrally read AIMS score (items 1 through 7) during the Randomized Withdrawal Period (from the Pre-withdrawal Visit to the Post-withdrawal Visit) will use an analysis of covariance (ANCOVA) model with the change in AIMS score as the dependent variable. The model will include randomized withdrawal treatment group, AIMS score at the Pre-withdrawal Visit, and DRA status at the Pre-withdrawal Visit as fixed effects. The least squares means of the change in AIMS score will be compared between the SD-809 treatment and placebo groups using a 2-sided test at the alpha=0.05 level of significance. In addition, actual values and changes in AIMS score will be summarized using descriptive	Added Section 8.6 for Efficacy Analysis of the Randomized Treatment Period

Section	Amendment 05 (dated 08 Feb 2017)	Amendment 06, dated 23 Jan 2018	Reason for Change
		statistics. The primary efficacy analysis will be tested at the α=0.05 level. If less than 135 subjects are enrolled into the randomized withdrawal portion of the study, inferential statistics will not be provided as the study will be insufficiently powered to detect a treatment effect given the sample size assumptions.	
Protocol Synopsis, Sample Size Section 8.7 Sample Size	Not applicable	During the Randomized Withdrawal Period, there will be up to 194 subjects randomized (SD-809 or placebo). It is estimated that approximately 91 subjects per arm will enable a power of at least 90% to detect a beneficial effect of 1.4 points or more in the change from pre-withdrawal to post-withdrawal in centrally read AIMS when the SD-809 arm is compared to placebo, assuming a standard deviation of 2.9 and a 2-sided type I error rate of 5%.	Updated to describe the Randomized Withdrawal Period sample
Section 9.1.2 Written Informed Consent	Not applicable	Part B Randomized Withdrawal Period Part B will begin after Amendment 06 implementation. Subjects who decline to participate in the Randomized Withdrawal Period (Part B) (i.e., sign written informed consent) will continue in Part A until Week 158.	Updated to include informed consent details for the Randomized Withdrawal Period
Appendix 22, Protocol Summary of Changes, Amendment 05 (dated 08 Feb 2017) to Amendment 06 (dated 23 Jan 2018)	Not applicable	Appendix added	Summarized protocol changes in Amendment 06
Global	Not applicable	Updated amendment number, dates, section numbers, and tables of contents. Corrected typos; errors in punctuation, grammar, and formatting; and inconsistencies in style.	

Appendix 23: Protocol Summary of Changes, Amendment 06 (dated 23 Jan 2018) to Amendment 07 (dated 02 May 2018)

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
Schedule of Events	First table designated as Part A and footnotes updated to reflect optional move to Part B; additional table created for Part B table. Columns include Part B Pre-withdrawal Visit, Part B Post-withdrawal Visit, EOT/ET visit, Follow-up visit (ET only), Follow-up Call, and Unscheduled.	Additional table created for Part C. Columns include Part C, EOT/ET visit, Follow-up clinical visit (ET only), Follow-up Call, and Unscheduled.	Updated to designate Part C
Study Schematic Diagram	Study Schematic Diagram (Parts A and B)	Study Schematic Diagram (Part C) Timeframe for Part B	Added study schematic diagram for Part C and the timeframe for Part B
Section 3 Investigational Plan	The study is divided into 2 parts, Part A and Part B. These parts include a Screening Period (Part A), a Titration Period (Part A), a Long-Term Treatment Period (Part A), a Double-Blind, Randomized Withdrawal Period (Part B), treatment after completion of the Randomized Withdrawal Period (Part B), and a Post-Treatment Safety Follow-up Period (Part A and Part B).	The study is divided into different parts: Part A and Part B for all countries and an additional Part C for the EU countries. These parts include a Screening Period (Part A), a Titration Period (Part A), a Long-Term Treatment Period (Part A), a Double-Blind, Randomized Withdrawal Period (Part B), treatment after completion of the Randomized Withdrawal Period (Part B), a continued treatment period (Part C), and a Post-Treatment Safety Follow-up Period (Part A, Part B, and Part C).	Updated study parts to include Part C
Protocol Synopsis, Section 3.1 Study Design	Informed consent/assent (Part A) will be obtained before any study procedures are performed. Subjects may have informed consent/assent obtained up to 30 days in advance of subject's parent study Week 13 Visit/TD-Long Term Safety (LTS) Baseline Visit. Subjects who meet the selection criteria will be eligible to participate. Informed consent/assent for Part B will be obtained after Amendment 06 implementation and before any study procedures related to Part B are performed.	Informed consent/assent for Part C will be obtained after Amendment 07 implementation and before any study procedures related to Part C are performed. Subjects who do not sign the informed consent/assent for Part C will complete the study at Part B Follow-up Call.	Updated to include informed consent for Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
Protocol Synopsis, Study Design	Not applicable	Part C: Part C will consist of a 52-week period of reduced burden safety assessments, for subjects in the EU countries. Subjects can only enter Part C once they have entered and completed Part B. The Part B EOT will coincide with Part C Visit 1 for those subjects who are willing to continue with the 52-week reduced burden safety assessment period. **Post-Treatment Safety Follow-up:** Subjects in EU countries may choose to enroll in Part C, in which case Part B EOT will coincide with Part C Visit 1. Part C: Subjects who complete the 52 weeks of reduced burden safety assessments period will complete a Part C EOT Visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since Part C EOT. Subjects who discontinue study drug in Part C will complete an ET visit, a follow-up clinic visit 1 week later for safety evaluation, and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.	Updated to include Part C and description of transition from Part B to Part C
Section 3.1 Study Design	Not applicable	Part C: For the EU countries, the study will include a reduced burden safety assessments period (Part C) of 52 weeks for subjects willing to continue in the study and who have completed Part B. Subjects will continue treatment with SD-809 at the current dose administered during the 12-week open-label period of Part B. Subjects will be scheduled to return every 13 weeks (±1 week) until EOT. A follow-up clinic visit will occur 1 week after ET and a follow-up telephone call will occur 4 weeks after EOT/ET. **Post-Treatment Safety Follow-up:** Part C:	Updated to include Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
		Subjects who complete the 52 weeks of reduced burden safety assessments period will complete a Part C EOT visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since Part C EOT. Subjects who discontinue study drug in Part C will complete an ET visit, a follow-up clinic visit 1 week later for safety evaluation, and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.	
Section 3.2 Rationale for Study Design	The study is designed to evaluate the long-term safety and tolerability of SD-809 in subjects with moderate to severe dyskinesia associated with TD (Part A) and the persistence or maintenance of the therapeutic effect of SD-809 in subjects with TD (Part B).	An extension of the study (Part C) with reduced burden safety assessments is added to provide continued therapy for subjects in the EU countries. Part C will be offered only to subjects who completed Part B.	Updated to include Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
Section 5.1 Study Drug	5.1 Study Drug 5.1.1 SD-809 During titration/dose adjustment, SD-809 tablets will be labeled according to applicable regulatory guidelines and supplied in weekly blister packs as 6, 9, 12, 15, and/or 18 mg tablets. Each blister pack will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies. **During long-term treatment, SD-809 will be supplied in 30-count bottles and labeled according to applicable regulatory guidelines.** During the 1-week Randomized Withdrawal Period, SD-809 will be supplied in 20-count bottles and labeled according to the applicable regulatory guidelines.	The study drug is a matrix formulation in the form of a tablet to be administered with food. Study drug is coated with a polymer coating to aid in swallowing. SD-809 tablets have been manufactured according to current Good Manufacturing Practices regulations. During titration/dose adjustment in Part A, SD-809 tablets will be labeled according to applicable regulatory guidelines and supplied in weekly blister packs as 6, 9, 12, 15, and/or 18 mg tablets. Each blister pack will contain a sufficient supply of study drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies. **During long-term treatment, SD-809 will be supplied in 30-count bottles and labeled according to applicable regulatory guidelines.** During the 1-week double blinded Randomized Withdrawal Period, SD-809 will be supplied in 20-count bottles and labeled according to the applicable regulatory guidelines. During Part C, SD-809 will be supplied in 30-count bottles. Complete details regarding SD-809 supply, dispensing, and ordering will be provided in the study Operations Manual. SD-809 tablets must be stored in a secure area with access limited to authorized staff, protected from light at controlled room temperature, 15°C to 25°C (59°F to 77°F).	Clarified the drug supply for Part A and Part C.
Section 5.2 Treatment Regimen	Daily doses up to 36 mg/day will be given as 1 tablet BID, whereas daily doses of 42, 48, 54, and 60 mg/day will be given as 2 tablets BID	Daily doses will be administered according to instructions provided in the Pharmacy Manual	Daily dosage was removed; added reference to the Pharmacy Manual.
Section 5.2.4 Dosing in Part C	Not applicable	**5.2.4 Dosing in Part C** The drug will be provided to study subjects in 30-count bottles. Each order will contain a sufficient supply of study drug until the next specified visit, plus overage to account for	Updated to include dosing details in Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change

potential delays in study visits or evaluations. Subjects who do not return for Part C Visit 1 within 10 days of completing the Part B EOT Visit may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary) per the guidelines in Table 4.

Table 4 Titration Schedule Part C End of Treatment Period (if Necessary)

Part B open-label period daily dose	1 week SD-809 titration daily dose (Step 1)	1 week SD-809 titration daily dose (Step 2)	SD-809 daily dose after completing titration
12 mg or placebo	N/A	N/A	12 mg
18 mg or placebo	12 mg	N/A	18 mg
24 mg or placebo	12 mg	N/A	24 mg
30 mg or placebo	18 mg	24 mg	30 mg
36 mg or placebo	18 mg	24 mg	36 mg
42 mg or placebo	24 mg	30mg	42 mg
48 mg or placebo	24 mg	36 mg	48 mg
54 mg or placebo	30 mg	42 mg	54 mg

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
		<table><tr><td>60 mg or placebo</td><td>30 mg</td><td>48mg</td><td>60 mg</td></tr></table> Abbreviation: mg, milligram; N/A, not applicable.	
Section 6.5 Reduced Burden Safety Assessments (Part C)	Not applicable	**Section 6.5 Reduced Burden Safety Assessments (Part C)** *See the Schedule of Events for a detailed summary of activities.* At Part C Visit 1, the subjects will undergo the activities performed at the Part B EOT visit as described above and will sign the informed consent/assent for Part C. At Part C Visit 2, Visit 3, Visit 4, or the EOT/ET Visit, subjects will undergo reduced burden safety assessments, including: • Physical examination, vital signs (including resting blood pressure and pulse), and weight • Complete neurological examination (Part C EOT/ET only) • Urine pregnancy test (done locally at the study site) • 12-lead ECG • C-SSRS: Since Last Visit version • Assessment of study drug accountability/compliance and collection of all study drug • Assessment of AEs and concomitant meds • Re-order study drug (see Operations Manual for further details, Part C Visit 2, Visit 3, and Visit 4) • The next clinic visit will be scheduled/reconfirmed Treatment with study drug will stop at the Part C EOT Visit.	Updated to include safety assessments in Part C
Section 6.6 Post-Treatment Safety Follow-Up	Following discontinuation of study drug at the EOT visit in Part B, subjects will have a telephone contact 4 weeks after	Following discontinuation of study drug at the EOT visit in Part B, subjects will have a telephone contact 4 weeks after the last dose of study drug to	Updated to clarify the transition to Part C and to include the safety follow-up in Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
	the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT. Following discontinuation of study drug at the ET visit in Part B, subjects will have a clinic visit 1 week later for evaluation of safety, dyskinesia, and motor function and a telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET. During the first week after stopping study drug, subjects should not take prohibited concomitant medications. Between the Week 158, EOT, or ET visit and the follow-up telephone contact, concomitant medication use is per the discretion of the Investigator.	evaluate the adverse events and concomitant medication use since EOT, unless they will continue with Part C. Following discontinuation of study drug at the ET visit in Part B, subjects will have a clinic visit 1 week later for evaluation of safety, dyskinesia, and motor function and a telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET. During the first week after stopping study drug, subjects should not take prohibited concomitant medications. Between the Week 158, EOT, or ET visit and the follow-up telephone contact, concomitant medication use is per the discretion of the Investigator. Subjects in Part C who complete the 52 weeks of reduced burden safety assessments period will complete a Part C EOT Visit and a follow-up telephone contact 4 weeks after the last dose of study drug, to evaluate the adverse events and concomitant medication use since Part C EOT. Subjects who discontinue study drug in Part C will complete an ET visit, a follow-up clinic visit 1 week later for safety evaluation, and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.	
Section 6.6.1 Clinic Visit (Week 159 ±3 Days or 1 Week after Early Termination ±3 Days)	All subjects will return 1 week after Week 158 (Part A) or the ET visit (Part A or Part B) for evaluation of safety, dyskinesia, and motor function. The following activities should be performed: • Assessment of adverse events, dyskinesia control (in consultation with the caregiver, if appropriate), and concomitant medication use • Vital signs	All subjects will return 1 week after the ET visit (Part C) for evaluation of safety. The following activities should be performed: • Assessment of adverse events and concomitant medication use • Vital signs • Weight • C-SSRS: Since Last Visit version • Next telephone contact will be scheduled/reconfirmed	Updated final clinic visit description to include Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
	• Weight • AIMS • UPDRS Part III (motor examination) • BARS • HADS • C-SSRS: Since Last Visit version • ESS • Next telephone contact will be scheduled/reconfirmed		
Section 6.6.2 Telephone Contact (4 Weeks After EOT/ET ± 3 Days)	6.5.2 Telephone Contact (Week 162 ± 3 Days or 4 Weeks After EOT/ET ± 3 Days) All subjects will have a follow-up telephone contact at Week 162 (4 weeks after their last dose of study drug [Week 158]) (Part A);	6.5.2 Telephone Contact (~~Week 162 ± 3 Days~~s 4 Weeks After EOT/ET ± 3 Days) All subjects will have a follow-up telephone contact ~~at Week 162 (~~4 weeks after their last dose of study drug [Week 158]) (Part A);	Removed Part A visit designator for the telephone contact
Section 6.6.2 Telephone Contact (4 Weeks After EOT/ET ± 3 Days)	All subjects will have a follow-up telephone contact at Week 162 (4 weeks after their last dose of study drug [Week 158]) (Part A); or 4 weeks after the EOT visit (Part B); or 4 weeks after the ET visit (Part A or Part B). During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about adverse events and concomitant medication use since the subject's last evaluation.	In Part C, all subjects will have a follow-up telephone contact 4 weeks after EOT/ET Visit (±3 days). During the telephone contact, subjects (and caregivers, if appropriate) will be questioned about adverse events and concomitant medication use since the subject's last evaluation.	Updated to include description of the telephone contact in Part C.
Section 6.7 Unscheduled Visit(s)	For **unscheduled clinic visit(s)** needed during the course of the study, the following activities should be performed, if indicated:	For **unscheduled clinic visit(s)** needed during Part A and Part B, the following activities should be performed, if indicated:	Added study parts designators for unscheduled clinic visits
Section 6.7 Unscheduled Visit(s)	For **unscheduled clinic visit(s)** needed during the course of the study, the following activities should be performed, if indicated: • Assessment of adverse events,	**For unscheduled clinic visit(s)** needed during Part C, the following activities should be performed, if indicated: • Vital signs and weight • 12-lead ECG at the Investigator's	Updated to include the description of unscheduled clinic visits in Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
	dyskinesia control (in consultation with the subject and caregiver), and concomitant medications • Vital signs and weight • 12-lead ECG at the Investigator's discretion • Clinical laboratory tests: serum chemistry, hematology, and urinalysis (at the Investigator's discretion) • Single pharmacokinetic (PK) blood sample (for Unscheduled Visits due to serious adverse event, within 48 hours, if possible) • UPDRS Part III (motor examination) (at the Investigator's discretion) • BARS (at the Investigator's discretion) • HADS • C-SSRS: Since Last Visit version • ESS (at the Investigator's discretion) • Evaluation of study drug dose level and adjustment, if necessary (at the Investigator's discretion) • Re-order study drug (at the Investigator's discretion)	discretion • C-SSRS: Since Last Visit version • Dispense study drug (at the Investigator discretion) • Assess AEs	
Section 6.7.2 Unscheduled Telephone Visit(s)	For **unscheduled telephone visit(s)** needed during the course of the study, the following activities should be performed	For **unscheduled telephone visit(s)** needed during ~~the course of the study~~Part A and Part B, the following activities should be performed	Added study parts designators for unscheduled telephone visits
Section 6.7.2 Unscheduled Telephone Visit(s)	For **unscheduled telephone visit(s)** needed during the course of the study, the following activities should be performed: • Assessment of adverse events, dyskinesia control, and concomitant medications in consultation with the	For unscheduled telephone visit(s) needed during Part C, the following activities should be performed: • Assessment of adverse events and concomitant medications in consultation with the subject and caregiver, if appropriate.	Updated to include the description of unscheduled telephone visits in Part C

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
	subject and caregiver, if appropriate. • Evaluation of study drug dose level and adjustment, if necessary (at the Investigator's discretion) • Re-order study drug (at the Investigator's discretion) (see Operations Manual for further details)		
Section 8.4 Safety Endpoints	The following safety endpoints will be assessed:	The following safety endpoints will be assessed in Part A:	Added study parts designator for safety endpoints
Section 8.4 Safety Endpoints	The following safety endpoints will be assessed: • Incidence of adverse events, serious adverse events, severe adverse events, drug-related adverse events, adverse events leading to withdrawal during the following periods: o Overall o During titration o During long-term treatment • Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes from baseline in vital signs • Observed values in ECG parameters and abnormal findings • Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms • Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C SSRS, ESS, and MoCA© • Duration of time to achieve stable dosing of SD-809 The following secondary safety	The following secondary safety endpoints will be assessed in Part C: • Secondary safety endpoints: o Incidence of adverse events, serious adverse events, severe adverse events, drug related adverse events, and adverse events leading to withdrawal from start of Part C o Observed values and changes in vital signs from start of Part C o Observed values and changes in C-SSRS from start of Part C o Observed values in ECG parameters and abnormal findings from start of Part C o Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms from start of Part C	Updated to include the safety endpoints for Part C

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	endpoints will be assessed in Part B: • Incidence of adverse events, serious adverse events, severe adverse events, drug related adverse events, and adverse events leading to withdrawal • Observed values and changes from start of randomized withdrawal in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes from start of randomized withdrawal in vital signs • Observed values in ECG parameters and abnormal findings • Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms, or a change from Baseline in QTcF of >30 ms or >60 ms • Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA©		
Section 8.7 Sample Size	During the Randomized Withdrawal Period, there will be up to 194 subjects randomized (SD-809 or placebo). It is estimated that approximately 91 subjects per arm will enable a power of at least 90% to detect a beneficial effect of 1.4 points or more in the change from pre-withdrawal to post-withdrawal in centrally read AIMS when the SD-809 arm is compared to placebo, assuming a standard deviation of 2.9 and a 2-sided type I error rate of 5%.	During the Randomized Withdrawal Period in Part B, there will be up to 194 subjects randomized (SD-809 or placebo). It is estimated that approximately 91 subjects per arm will enable a power of at least 90% to detect a beneficial effect of 1.4 points or more in the change from pre-withdrawal to post-withdrawal in centrally read AIMS when the SD-809 arm is compared to placebo, assuming a standard deviation of 2.9 and a 2-sided type I error rate of 5%. Approximately 102 subjects may enroll in Part C conducted in the EU countries.	Added study part designators for the sample size and the estimated sample size for Part C
Section 9.1.2 Written Informed Consent	Informed consent will be obtained before the subject can participate in the study. If subject lacks the capacity to provide informed consent, a LAR must provide written informed consent and	Part C Reduced Burden Safety Assessments Part C will begin after Amendment 07 implementation. Subjects who decline to participate in Part C (i.e., do not sign written informed consent) will complete the study at the	Updated to include the informed consent procedures in Part C

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	the subject must provide assent. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements. It is the responsibility of the Investigator or designee to obtain written informed consent, using the most current informed consent form approved by the IRB/IEC and Sponsor, from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator or designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting written consent will be provided by the Investigator or designee. For this study, each eligible subject will be required to provide written informed consent utilizing: Consent to participation in the study (Information Form/Informed Consent Form). All eligible subjects and caregivers will have the study explained by the Investigator or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomfort, risks, and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from	Part B Follow up Call.	

Section	Amendment 06, dated 23 Jan 2018	Amendment 07, dated 02 May 2018	Reason for Change
	the study at any time without prejudice. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study. The subject and caregiver will be given a copy of the signed Information Form/Informed Consent Form to retain. Part B Double-Blind, Randomized Withdrawal Period Part B will begin after Amendment 06 implementation. Subjects who decline to participate in the Randomized Withdrawal Period (Part B) (i.e., sign written informed consent) will continue in Part A until Week 158.		
Global	Not applicable	Updated amendment number, dates, section numbers, and tables of contents. Corrected typos; errors in punctuation, grammar, and formatting; and inconsistencies in style.	